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(57) Abstract: The present invention relates to peptides which exhibit potent anti-retroviral activity. The peptides of the invention comprise DP178 (SEQ ID:1) peptide corresponding to amino acids 638 to 673 of the HIV-1_{LAI} gp41 protein, and fragments, analogs and homologs of DP178. The invention further relates to the uses of such peptides as inhibitory of human and non-human retroviral, especially HIV, transmission to uninfected cells.

METHODS AND COMPOSITIONS FOR INHIBITION OF MEMBRANE FUSION-ASSOCIATED EVENTS, INCLUDING HIV TRANSMISSION

1. INTRODUCTION

The present invention relates, first, to DP178 (SEQ ID NO:1), a peptide, also referred to herein as T20, corresponding to amino acids 638 to 673 of the HIV-1_{LAI} transmembrane protein (TM) gp41, and portions or analogs of DP178 (SEQ ID NO:1), which exhibit anti-membrane fusion capability, antiviral activity, such as the ability to inhibit HIV transmission to uninfected CD-4$^+$ cells, or an ability to modulate intracellular processes involving coiled-coil peptide structures. The present invention also relates to peptides analogous to DP107 (SEQ ID NO:25), a peptide, which is also referred to herein as T21, corresponding to amino acids 558 to 595 of the HIV-1_{LAI} transmembrane protein (TM) gp41, having amino acid sequences present in other viruses, such as enveloped viruses, and/or other organisms, and further relates to the uses of such peptides. These peptides exhibit anti-membrane fusion capability, antiviral activity, or the ability to modulate intracellular processes involving coiled-coil peptide structures.

The gp41 region from which DP107 is derived is referred to herein as HR1. The gp41 region from which DP178 is derived is referred to herein as HR2. As discussed herein, the gp41 HR1 and HR2 regions interact (non-covalently) with each other and/or with

T20 and T21 peptides. This interaction is required for normal infectivity of HIV.

The present invention therefore additionally relates to methods for identifying compounds, including small molecule compounds, that disrupt the interaction between DP178 and DP107, and/or between DP107-like and DP178-like peptides. In one embodiment, such methods relate to identification and utilization of modified DP178, DP178-like, DP107 and DP107-like peptides and peptide pairs that interact with each other at a lower affinity than the affinity exhibited by corresponding "parent" or "native" peptides. Further, the invention relates to the use of DP178, DP178 portions, DP107, DP017 portions and/or analogs and other modulators, including small molecules modulators, of DP178/DP107, DP178-like/DP107-like, or HR1/HR2 interactions as antifusogenic or antiviral compounds or as inhibitors of intracellular events involving coiled-coil peptide structures. The invention is demonstrated, first, by way of an Example wherein DP178 (SEQ ID:1), and a peptide whose sequence is homologous to DP178 are each shown to be potent, non-cytotoxic inhibitors of HIV-1 transfer to uninfected CD-4$^+$ cells. The invention is further demonstrated by Examples wherein peptides having structural and/or amino acid motif similarity to DP107 and DP178 are identified in a variety of viral and nonviral organisms, and in examples wherein a number of such identified peptides derived from several different viral systems are demonstrated to exhibit antiviral activity. The invention is still further demonstrated by way of Examples wherein other DP178-like and DP107-like peptides are identified that

interact with their corresponding HR1 and HR2 domains with a lower affinity than the affinity exhibited by the native DP178 or DP107 peptide from which they are derived.

2. BACKGROUND OF THE INVENTION

2.1 MEMBRANE FUSION EVENTS

Membrane fusion is a ubiquitous cell biological process (for a review, see White, J.M., 1992, Science 258:917-924). Fusion events which mediate cellular housekeeping functions, such as endocytosis, constitutive secretion, and recycling of membrane components, occur continuously in all eukaryotic cells.

Additional fusion events occur in specialized cells. Intracellularly, for example, fusion events are involved in such processes as occur in regulated exocytosis of hormones, enzymes and neurotransmitters. Intercellularly, such fusion events feature prominently in, for example, sperm-egg fusion and myoblast fusion.

Fusion events are also associated with disease states. For example, fusion events are involved in the formation of giant cells during inflammatory reactions, the entry of all enveloped viruses into cells, and, in the case of human immunodeficiency virus (HIV), for example, are responsible for the virally induced cell-cell fusion which leads to cell death.

2.2. THE HUMAN IMMUNODEFICIENCY VIRUS

The human immunodeficiency virus (HIV) has been implicated as the primary cause of the slowly

degenerative immune system disease termed acquired immune deficiency syndrome (AIDS) (Barre-Sinoussi, F. et al., 1983, Science 220:868-870; Gallo, R. et al., 1984, Science 224:500-503). There are at least two distinct types of HIV: HIV-1 (Barre-Sinoussi, F. et al., 1983, Science 220:868-870; Gallo R. et al., 1984, Science 224:500-503) and HIV-2 (Clavel, F. et al., 1986, Science 233:343-346; Guyader, M. et al., 1987, Nature 326:662-669). Further, a large amount of genetic heterogeneity exists within populations of each of these types. Infection of human CD-4+ T-lymphocytes with an HIV virus leads to depletion of the cell type and eventually to opportunistic infections, neurological dysfunctions, neoplastic growth, and ultimately death.

HIV is a member of the lentivirus family of retroviruses (Teich, N. et al., 1984, RNA Tumor Viruses, Weiss, R. et al., eds., CSH-Press, pp. 949-956). Retroviruses are small enveloped viruses that contain a diploid, single-stranded RNA genome, and replicate via a DNA intermediate produced by a virally-encoded reverse transcriptase, an RNA-dependent DNA polymerase (Varmus, H., 1988, Science 240:1427-1439). Other retroviruses include, for example, oncogenic viruses such as human T-cell leukemia viruses (HTLV-I,-II,-III), and feline leukemia virus.

The HIV viral particle consists of a viral core, composed of capsid proteins, that contains the viral RNA genome and those enzymes required for early replicative events. Myristylated Gag protein forms an outer viral shell around the viral core, which is, in turn, surrounded by a lipid membrane enveloped derived

from the infected cell membrane. The HIV enveloped surface glycoproteins are synthesized as a single 160 Kd precursor protein which is cleaved by a cellular protease during viral budding into two glycoproteins, gp41 and gp120. gp41 is a transmembrane protein and gp120 is an extracellular protein which remains non-covalently associated with gp41, possibly in a trimeric or multimeric form (Hammarskjold, M. and Rekosh, D., 1989, Biochem. Biophys. Acta 989:269-280).

HIV is targeted to CD-4$^+$ cells because the CD-4 cell surface protein acts as the cellular receptor for the HIV-1 virus (Dalgleish, A. et al., 1984, Nature 312:763-767; Klatzmann et al., 1984, Nature 312:767-768; Maddon et al., 1986, Cell 47:333-348). Viral entry into cells is dependent upon gp120 binding the cellular CD-4$^+$ receptor molecules (McDougal, J.S. et al., 1986, Science 231:382-385; Maddon, P.J. et al., 1986, Cell 47:333-348) and thus explains HIV's tropism for CD-4$^+$ cells, while gp41 anchors the enveloped glycoprotein complex in the viral membrane.

2.3. HIV TREATMENT

HIV infection is pandemic and HIV associated diseases represent a major world health problem. Although considerable effort is being put into the successful design of effective therapeutics, currently no curative anti-retroviral drugs against AIDS exist. In attempts to develop such drugs, several stages of the HIV life cycle have been considered as targets for therapeutic intervention (Mitsuya, H. et al., 1991, FASEB J. 5:2369-2381). For example, virally encoded reverse transcriptase has been one focus of drug development. A number of reverse-transcriptase-

targeted drugs, including 2',3'-dideoxynucleoside analogs such as AZT, ddI, ddC, and d4T have been developed which have been shown to been active against HIV (Mitsuya, H. et al., 1991, Science 249:1533-1544). While beneficial, these nucleoside analogs are not curative, probably due to the rapid appearance of drug resistant HIV mutants (Lander, B. et al., 1989, Science 243:1731-1734). In addition, the drugs often exhibit toxic side effects such as bone marrow suppression, vomiting, and liver function abnormalities.

Attempts are also being made to develop drugs which can inhibit viral entry into the cell, the earliest stage of HIV infection. Here, the focus has thus far been on CD4, the cell surface receptor for HIV. Recombinant soluble CD4, for example, has been shown to inhibit infection of CD-4+ T-cells by some HIV-1 strains (Smith, D.H. et al., 1987, Science 238:1704-1707). Certain primary HIV-1 isolates, however, are relatively less sensitive to inhibition by recombinant CD-4 (Daar, E. et al., 1990, Proc. Natl. Acad. Sci. USA 87:6574-6579). In addition, recombinant soluble CD-4 clinical trials have produced inconclusive results (Schooley, R. et al., 1990, Ann. Int. Med. 112:247-253; Kahn, J.O. et al., 1990, Ann. Int. Med. 112:254-261; Yarchoan, R. et al., 1989, Proc. Vth Int. Conf. on AIDS, p. 564, MCP 137).

The late stages of HIV replication, which involve crucial virus-specific secondary processing of certain viral proteins, have also been suggested as possible anti-HIV drug targets. Late stage processing is dependent on the activity of a viral protease, and drugs are being developed which inhibit this protease

(Erickson, J., 1990, Science 249:527-533). The clinical outcome of these candidate drugs is still in question.

Attention is also being given to the development of vaccines for the treatment of HIV infection. The HIV-1 enveloped proteins (gp160, gp120, gp41) have been shown to be the major antigens for anti-HIV antibodies present in AIDS patients (Barin, et al., 1985, Science 228:1094-1096). Thus far, therefore, these proteins seem to be the most promising candidates to act as antigens for anti-HIV vaccine development. To this end, several groups have begun to use various portions of gp160, gp120, and/or gp41 as immunogenic targets for the host immune system. See for example, Ivanoff, L. et al., U.S. Pat. No. 5,141,867; Saith, G. et al., WO 92/22,654; Shafferman, A., WO 91/09,872; Formoso, C. et al., WO 90/07,119. Clinical results concerning these candidate vaccines, however, still remain far in the future.

Thus, although a great deal of effort is being directed to the design and testing of anti-retroviral drugs, a truly effective, non-toxic treatment is still needed.

3. SUMMARY OF THE INVENTION

The present invention relates, first, to DP178, a 36-amino acid synthetic peptide, also referred to herein as T20, corresponding to amino acids 638 to 673 of the transmembrane protein (TM) gp41 from the HIV-1 isolate LAI (HIV-1_{LAI}), which exhibits potent anti-HIV-1 activity. The gp41 region from which DP178 is derived in referred to herein as HR2.

The invention further relates to those portions and analogs of DP178 which also show such antiviral activity, and/or show anti-membrane fusion capability, or an ability to modulate intracellular processes involving coiled-coil peptide structures. The term "DP178 analog" refers to a peptide which contains an amino acid sequence corresponding to the DP178 peptide sequence present within the gp41 protein of HIV-1_{LAI}, but found in viruses and/or organisms other than HIV-1_{LAI}. Such DP178 analog peptides may, therefore, correspond to DP178-like amino acid sequences present in other viruses, such as, for example, enveloped viruses, such as retroviruses other than HIV-1_{LAI}, as well as non-enveloped viruses. Further, such analogous DP178 peptides may also correspond to DP178-like amino acid sequences present in nonviral organisms.

The invention further relates to DP107, a peptide, which is also referred to herein as T21, corresponding to amino acids 558-595 of the HIV-1_{LAI} transmembrane protein (TM) gp41. The gp41 region from which DP107 is derived is referred to herein as HR1. The invention also relates to those portions and analogs of DP107 which that also show antiviral activity, and/or show anti-membrane fusion capability, or an ability to modulate intracellular processes involving coiled-coil peptide structures. The term "DP107 analog" as used herein refers to a peptide which contains an amino acid sequence corresponding to the DP107 peptide sequence present within the gp41 protein of HIV-1_{LAI}, but found in viruses and organisms other than HIV-1_{LAI}. Such DP107 analog peptides may, therefore, correspond to DP107-like amino acid

sequences present in other viruses, such as, for for example, enveloped viruses, such as retroviruses other than HIV-1_{LAI}, as well as non-enveloped viruses. Further, such DP107 analog peptides may also correspond to DP107-like amino acid sequences present in nonviral organisms.

Further, the peptides of the invention include DP107 analog and DP178 analog peptides having amino acid sequences recognized or identified by the 107x178x4, ALLMOTI5 and/or PLZIP search motifs described herein.

The peptides of the invention may, for example, exhibit antifusogenic activity, antiviral activity, and/or may have the ability to modulate intracellular processes which involve coiled-coil peptide structures. With respect to the antiviral activity of the peptides of the invention, such an antiviral activity includes, but is not limited to the inhibition of HIV transmission to uninfected CD-4+ cells. Additionally, the antifusogenic capability, antiviral activity or intracellular modulatory activity of the peptides of the invention merely requires the presence of the peptides of the invention, and, specifically, does not require the stimulation of a host immune response directed against such peptides.

The peptides of the invention may be used, for example, as inhibitors of membrane fusion-asociated events, such as, for example, the inhibition of human and non-human retroviral, especially HIV, transmission to uninfected cells. It is further contemplated that the peptides of the invention may be used as

modulators of intracellular events involving coiled-coil peptide structures.

The peptides of the invention may, alternatively, be used to identify compounds, including small molecule compounds, which may themselves exhibit antifusogenic, antiviral, or intracellular modulatory activity. For example, in one embodiment, the peptides of the invention are used to identify other DP178-like and/or DP107-like peptides that interact with each other and/or with their complementary HR1 or HR2 domains with a lower affinity than the affinity exhibited by the "parent" or "native" DP178 or DP107 peptides from which they are derived. Such DP178-like and DP107-like peptides, which are also part of the present invention, may also be used, *e.g.*, to identify compounds, such as small molecule compounds, that exhibit antifusogenic, antiviral, or intracellular modulatory activity.

Additional uses include, for example, the use of the peptides of the invention as organism or viral type and/or subtype-specific diagnostic tools.

The terms "antifusogenic" and "anti-membrane fusion", as used herein, refer to an agent's ability to inhibit or reduce the level of membrane fusion events between two or more moieties relative to the level of membrane fusion which occurs between said moieties in the absence of the peptide. The moieties may be, for example, cell membranes or viral structures, such as viral envelopes or pili. The term "antiviral", as used herein, refers to the compound's ability to inhibit viral infection of cells, via, for example, cell-cell fusion or free virus infection. Such infection may involve membrane fusion, as occurs

in the case of enveloped viruses, or some other fusion event involving a viral structure and a cellular structure (e.g., such as the fusion of a viral pilus and bacterial membrane during bacterial conjugation).

It is also contemplated that the peptides of the invention may exhibit the ability to modulate intracellular events involving coiled-coil peptide structures. "Modulate", as used herein, refers to a stimulatory or inhibitory effect on the intracellular process of interest relative to the level or activity of such a process in the absence of a peptide of the invention.

Embodiments of the invention are demonstrated below wherein an extremely low concentration of DP178 (SEQ ID:1), and very low concentrations of a DP178 homolog (SEQ ID:3) are shown to be potent inhibitors of HIV-1 mediated CD-4$^+$ cell-cell fusion (i.e., syncytial formation) and infection of CD-4$^+$ cells by cell-free virus. Further, it is shown that DP178 (SEQ ID:1) is not toxic to cells, even at concentrations 3 logs higher than the inhibitory DP-178 (SEQ ID:1) concentration.

The present invention is based, in part, on the surprising discovery that the DP107 and DP178 domains of the HIV gp41 protein non-covalently complex with each other, and that their interaction is required for the normal infectivity of the virus. This discovery is described in the Example presented, below, in Section 8. The invention, therefore, further relates to methods for identifying antifusogenic, including antiviral, compounds that disrupt the interaction between DP107 and DP178, and/or between DP107-like and DP178-like peptides.

Additional embodiments of the invention (specifically, the Examples presents in Sections 9-16 and 19-25, below) are demonstrated, below, wherein peptides, from a variety of viral and nonviral sources, having structural and/or amino acid motif similarity to DP107 and DP178 are identified, and search motifs for their identification are described. Further, Examples (in Sections 17, 18, 25-29) are presented wherein a number of the peptides of the invention are demonstrated exhibit substantial antiviral activity or activity predictive of antiviral activity.

3.1. DEFINITIONS

Peptides are defined herein as organic compounds comprising two or more amino acids covalently joined by peptide bonds. Peptides may be referred to with respect to the number of constituent amino acids, i.e., a dipeptide contains two amino acid residues, a tripeptide contains three, etc. Peptides containing ten or fewer amino acids may be referred to as oligopeptides, while those with more than ten amino acid residues are polypeptides. Such peptides may also include any of the modifications and additional amino and carboxy groups as are described herein.

Peptide sequences defined herein are represented by one-letter symbols for amino acid residues as follows:

A (alanine)
R (arginine)
N (asparagine)
D (aspartic acid)
C (cysteine)
Q (glutamine)
E (glutamic acid)

G (glycine)
H (histidine)
I (isoleucine)
L (leucine)
K (lysine)
M (methionine)
F (phenylalanine)
P (proline)
S (serine)
T (threonine)
W (tryptophan)
Y (tyrosine)
V (valine)

4. BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. Amino acid sequence of DP178 (SEQ ID:1) derived from HIV_{LAI}; DP178 homologs derived from HIV-1_{SF2} (DP-185; SEQ ID:3), HIV-1_{RF} (SEQ ID:4), and HIV-1_{MN} (SEQ ID:5); DP178 homologs derived from amino acid sequences of two prototypic HIV-2 isolates, namely, HIV-2_{rod} (SEQ ID:6) and HIV-2_{NIHZ} (SEQ ID:7); control peptides: DP-180 (SEQ ID:2), a peptide incorporating the amino acid residues of DP178 in a scrambled sequence; DP-118 (SEQ ID:10) unrelated to DP178, which inhibits HIV-1 cell free virus infection; DP-125 (SEQ ID:8), unrelated to DP178, also inhibits HIV-1 cell free virus infection; DP-116 (SEQ ID:9), unrelated to DP178, is negative for inhibition of HIV-1 infection when tested using a cell-free virus infection assay. Throughout the figures, the one letter amino acid code is used.

FIG. 2. Inhibition of HIV-1 cell-free virus infection by synthetic peptides. IC_{50} refers to the concentration of peptide that inhibits RT production from infected cells by 50% compared to the untreated control. Control: the level of RT produced by

untreated cell cultures infected with the same level of virus as treated cultures.

FIG. 3. Inhibition of HIV-1 and HIV-2 cell-free virus infection by the synthetic peptide DP178 (SEQ ID:1). IC_{50}: concentration of peptide that inhibits RT production by 50% compared to the untreated control. Control: Level of RT produced by untreated cell cultures infected with the same level of virus as treated cultures.

FIG. 4A-4B. Fusion Inhibition Assays. FIG 4A: DP178 (SEQ ID:1) inhibition of HIV-1 prototypic isolate-mediated syncytial formation; data represents the number of virus-induced syncytial per cell. FIG. 4B: DP-180 (SEQ ID:2) represents a scrambled control peptide; DP-185 (SEQ ID:3) represents a DP178 homolog derived from HIV-1_{SF2} isolate; Control, refers to the number of syncytial produced in the absence of peptide.

FIG. 5. Fusion inhibition assay: HIV-1 vs. HIV-2. Data represents the number of virus-induced syncytial per well. ND: not done.

FIG. 6. Cytotoxicity study of DP178 (SEQ ID:1) and DP-116 (SEQ ID:9) on CEM cells. Cell proliferation data is shown.

FIG. 7. Schematic representation of HIV-gp41 and maltose binding protein (MBP)-gp41 fusion proteins. DP107 and DP178 are synthetic peptides based on the two putative helices of gp41. The letter P in the DP107 boxes denotes an Ile to Pro mutation at amino acid number 578. Amino acid residues are numbered according to Meyers et al., "Human Retroviruses and AIDS", 1991, Theoret. Biol. and Biophys. Group, Los Alamos Natl. Lab., Los Alamos, NM.

The proteins are more fully described, below, in Section 8.1.1.

FIG. 8. A point mutation alters the conformation and anti-HIV activity of M41.

FIG. 9. Abrogation of DP178 anti-HIV activity. Cell fusion assays were carried out in the presence of 10 nM DP178 and various concentrations of M41Δ178 or M41PΔ178.

FIG. 10. Binding of DP178 to leucine zipper of gp41 analyzed by FAb-D ELISA.

FIG. 11A-B. Models for a structural transition in the HIV-1 TM protein. Two models are proposed which indicate a structural transition from a native oligomer to a fusogenic state following a trigger event (possibly gp120 binding to CD4). Common features of both models include (1) the native state is held together by noncovalent protein-protein interactions to form the heterodimer of gp120/41 and other interactions, principally though gp41 interactive sites, to form homo-oligomers on the virus surface of the gp120/41 complexes; (2) shielding of the hydrophobic fusogenic peptide at the N-terminus (F) in the native state; and (3) the leucine zipper domain (DP107) exists as a homo-oligomer coiled coil only in the fusogenic state. The major differences in the two models include the structural state (native or fusogenic) in which the DP107 and DP178 domains are complexed to each other. In the first model (FIG. 11A) this interaction occurs in the native state and in the second (FIG. 11B), it occurs during the fusogenic state. When triggered, the fusion complex in the model depicted in (A) is generated through formation of coiled-coil interactions in homologous

DP107 domains resulting in an extended α-helix. This conformational change positions the fusion peptide for interaction with the cell membrane. In the second model (FIG. 11B), the fusogenic complex is stabilized by the association of the DP178 domain with the DP107 coiled-coil.

FIG. 12. Motif design using heptad repeat positioning of amino acids of known coiled-coils.

FIG. 13. Motif design using proposed heptad repeat positioning of amino acids of DP107 and DP178.

FIG. 14. Hybrid motif design crossing GCN4 and DP107.

FIG. 15. Hybrid motif design crossing GCN4 and DP178.

FIG. 16. Hybrid motif design 107x178x4, crossing DP107 and DP178. This motif was found to be the most consistent at identifying relevant DP107-like and DP178-like peptide regions.

FIG. 17. Hybrid motif design crossing GCN4, DP107, and DP178.

FIG. 18. Hybrid motif design ALLMOTI5 crossing GCN4, DP107, DP178, c-Fos c-Jun, c-Myc, and Flu Loop 36.

FIG. 19. PLZIP motifs designed to identify N-terminal proline-leucine zipper motifs.

FIG. 20. Search results for HIV-1 (BRU isolate) enveloped protein gp41. Sequence search motif designations: Spades (♠): 107x178x4; Hearts (♥) ALLMOTI5; Clubs (♣): PLZIP; Diamonds (♦): transmembrane region (the putative transmembrane domains were identified using a PC/Gene program designed to search for such peptide regions). Asterisk (*): Lupas method. The amino acid sequences

identified by each motif are bracketed by the respective characters. Representative sequences chosen based on 107x178x4 searches are underlined and in bold. DP107 and DP178 sequences are marked, and additionally double-underlined and italicized.

FIG. 21. Search results for human respiratory syncytial virus (RSV) strain A2 fusion glycoprotein F1. Sequence search motif designations are as in FIG. 20.

FIG. 22. Search results for simian immunodeficiency virus (SIV) enveloped protein gp41 (AGM3 isolate). Sequence search motif designations are as in FIG. 20.

FIG. 23. Search results for canine distemper virus (strain Onderstepoort) fusion glycoprotein 1. Sequence search motif designations are as in FIG. 20.

FIG. 24. Search results for newcastle disease virus (strain Australia-Victoria/32) fusion glycoprotein F1. Sequence search motif designations are as in FIG. 20.

FIG. 25. Search results for human parainfluenza 3 virus (strain NIH 47885) fusion glycoprotein F1. Sequence search motif designations are as in FIG. 20.

FIG. 26. Search results for influenza A virus (strain A/AICHI/2/68) hemagglutinin precursor HA2. Sequence search designations are as in FIG. 20.

FIG. 27A-D. Respiratory Syncytial Virus (RSV) peptide antiviral and circular dichroism data. FIG. 27A-B: Peptides derived from the F2 DP178/DP107-like region. Antiviral and CD data. FIG. 27C-D:

Peptides derived from the F1 DP107-like region. Peptide and CD data.

Antiviral activity (AV) is represented by the following qualitative symbols:

"-", negative antiviral activity;

"+/-", antiviral activity at greater than 100μg/ml;

"+", antiviral activity at between 50-100μg/ml;

"++", antiviral activity at between 20-50μg/ml;

"+++", antiviral activity at between 1-20μg/ml;

"++++", antiviral activity at <1μg/ml.

CD data, referring to the level of helicity is represented by the following qualitative symbol:

"-", no helicity;

"+", 25-50% helicity;

"++", 50-75% helicity;

"+++"' 75-100% helicity.

IC_{50} refers to the concentration of peptide necessary to produce only 50% of the number of syncytial relative to infected control cultures containing no peptide. IC_{50} values were obtained using purified peptides only.

FIG. 28A-B. Respiratory Syncytial Virus (RSV) DP178-like region (F1) peptide antiviral and CD data. Antiviral symbols, CD symbols, and IC_{50} are as in FIG. 27A-D. IC_{50} values were obtained using purified peptides only.

FIG. 29A-B. Peptides derived from the HPIV3 F1 DP107-like region. Peptide antiviral and CD data. Antiviral symbols, CD symbols, and IC_{50} are as in FIG. 27A-D. Purified peptides were used to obtain IC_{50} values, except where the values are marked by an

asterisk (*), in which cases, the IC_{50} values were obtained using a crude peptide preparation.

FIG. 29C. HPIV3 peptide T-184 CD spectrum at 1°C in 0.1M NaCl 10mM KPO_4, pH 7.0. The data demonstrates the peptide's helical secondary structure ($\theta_{222/208}$=1.2) over a wide range of concentrations (100-1500μM). This evidence is consistent with the peptide forming a helical coiled-coil structure.

FIG. 30A-B. Peptides derived from the HPIV3 F1 DP178-like region. Peptide antiviral and CD data. Antiviral symbols, CD symbols, and IC_{50} are as in FIG. 27A-D. Purified peptides were used to obtain IC_{50} values, except where the values are marked by an asterisk (*), in which cases, the IC_{50} values were obtained using a crude peptide preparation.

FIG. 31. Motif search results for simian immunodeficiency virus (SIV) isolate MM251, enveloped polyprotein gp41. Sequence search designations are as in FIG. 20.

FIG. 32. Motif search results for Epstein-Barr Virus (Strain B95-8), glycoprotein gp110 precursor (designated gp115). BALF4. Sequence search designations are as in FIG. 20.

FIG. 33. Motif search results for Epstein-Barr Virus (Strain B95-8), BZLF1 trans-activator protein (designated EB1 or Zebra). Sequence search designations are as in FIG. 20. Additionally, "@" refers to a well known DNA binding domain and "+" refers to a well known dimerization domain, as defined by Flemington and Speck (Flemington, E. and Speck, S.H., 1990, Proc. Natl. Acad. Sci. USA 87:9459-9463).

FIG. 34. Motif search results for measles

virus (strain Edmonston), fusion glycoprotein F1. Sequence search designations are as in FIG. 20.

FIG. 35. Motif search results for Hepatitis B Virus (Subtype AYW), major surface antigen precursor S. Sequence search designations are as in FIG. 20.

FIG. 36. Motif search results for simian Mason-Pfizer monkey virus, enveloped (TM) protein gp20. Sequence search designations are as in FIG. 20.

FIG. 37. Motif search results for Pseudomonas aerginosa, fimbrial protein (Pilin). Sequence search designations are as in FIG. 20.

FIG. 38. Motif search results for Neisseria gonorrhoeae fimbrial protein (Pilin). Sequence search designations are as in FIG. 20.

FIG. 39. Motif search results for Hemophilus influenzae fimbrial protein. Sequence search designations are as in FIG. 20.

FIG. 40. Motif search results for Staphylococcus aureus, toxic shock syndrome toxin-1. Sequence search designations are as in FIG. 20.

FIG. 41. Motif search results for Staphylococcus aureus enterotoxin Type E. Sequence search designations are as in FIG. 20.

FIG. 42. Motif search results for Staphylococcus aureus enterotoxin A. Sequence search designations are as in FIG. 20.

FIG. 43. Motif search results for Escherichia coli, heat labile enterotoxin A. Sequence search designations are as in FIG. 20.

FIG. 44. Motif search results for human c-fos proto-oncoprotein. Sequence search designations are as in FIG. 20.

FIG. 45. Motif search results for human lupus KU autoantigen protein P70. Sequence search designations are as in FIG. 20.

FIG. 46. Motif search results for human zinc finger protein 10. Sequence search designations are as in FIG. 20.

FIG. 47. Measles virus (MeV) fusion protein DP178-like region antiviral and CD data. Antiviral symbols, CD symbols, and IC_{50} are as in FIG. 27A-D. IC_{50} values were obtained using purified peptides.

FIG. 48. Simian immunodeficiency virus (SIV) TM (fusion) protein DP178-like region antiviral data. Antiviral symbols are as in FIG. 27A-D "NT", not tested.

FIG. 49A-C. DP178-derived peptide antiviral data. The peptides listed herein were derived from the region surrounding the HIV-1 BRU isolate DP178 region (e.g., gp41 amino acid residues 615-717).

In instances where peptides contained DP178 point mutations, the mutated amino acid residues are shown with a shaded background. In instances in which the test peptide has had an amino and/or carboxy-terminal group added or removed (apart from the standard amido- and acetyl- blocking groups found on such peptides), such modifications are indicated. FIG. 49A: The column to the immediate right of the name of the test peptide indicates the size of the test peptide and points out whether the peptide is derived from a one amino acid peptide "walk" across the DP178 region. The next column to the right indicates whether the test peptide contains a point mutation, while the column to its right indicates whether certain amino acid residues have been added to or removed from the

DP178-derived amino acid sequence. FIG 49B: The column to the immediate right of the test peptide name indicates whether the peptide represents a DP178 truncation, the next column to the right points out whether the peptide contains a point mutation, and the column to its right indicates whether the peptide contains amino acids which have been added to or removed from the DP178 sequence itself. FIG. 49C: The column to the immediate right of the test peptide name indicates whether the test peptide contains a point mutation, while the column to its right indicates whether amino acid residues have been added to or removed from the DP178 sequence itself. IC_{50} is as defined in FIG. 27A-D, and IC_{50} values were obtained using purified peptides except where marked with an asterisk (*), in which case the IC_{50} was obtained using a crude peptide preparation.

FIG. 50. DP107 and DP107 gp41 region truncated peptide antiviral data. IC_{50} as defined in FIG. 27A-D, and IC_{50} values were obtained using purified peptides except where marked with an asterisk (*), in which case the IC_{50} was obtained using a crude peptide preparation.

FIG. 51A-B. Epstein-Barr virus Strain B95-8 BZLF1 DP178/DP107 analog region peptide walks and electrophoretic mobility shift assay results. The peptides (T-423 to T-446, FIG. 51A; T-447 to T-461, FIG. 51B) represent one amino acid residue "walks" through the EBV Zebra protein region from amino acid residue 173 to 246.

The amino acid residue within this region which corresponds to the first amino acid residue of each peptide is listed to the left of each peptide, while

the amino acid residue within this region which corresponds to the last amino acid residue of each peptide is listed to the right of each peptide. The length of each test peptide is listed at the far right of each line, under the heading "Res".

"ACT" refers to a test peptide's ability to inhibit Zebra binding to its response element. "+" refers to a visible, but incomplete, abrogation of the response element/Zebra homodimer complex; "+++" refers to a complete abrogation of the complex; and "-" represents a lack of complex disruption.

FIG. 52A-B. Hepatitis B virus subtype AYW major surface antigen precursor S protein DP178/DP107 analog region and peptide walks. 52A depicts Domain I (S protein amino acid residues 174-220), which contains a potential DP178/DP107 analog region. In addition, peptides are listed which represent one amino acid peptide "walks" through domain I. 52B depicts Domain II (S protein amino acid residues 233-291), which contains a second potential DP178/DP107 analog region. In addition, peptides are listed which represent one amino acid peptide "walks" through domain II.

FIG. 53: Cell fusion and competitive inhibition data for alanine walk experiments for the DP178-like Respiratory Syncytial Virus (RSV) peptide T112.

FIG. 54: Circular dichroism, cell fusion and competitive inhibition data for alanine walk experiments for the peptide T20, which is also known as DP178.

5. DETAILED DESCRIPTION OF THE INVENTION

Described herein are peptides which may exhibit antifusogenic activity, antiviral capability, and/or

the ability to modulate intracellular processes involving coiled-coil peptide structures. The peptides described include, first, DP178 (SEQ ID NO:1), a gp41-derived 36 amino acid peptide and fragments and analogs of DP178.

In addition, the peptides of the invention described herein include peptides which are DP107 analogs. DP107 (SEQ ID NO:25) is a 38 amino acid peptide corresponding to residues 558 to 595 of the HIV-1_{LAI} transmembrane (TM) gp41 protein. Such DP107 analogs may exhibit antifusogenic capability, antiviral activity or an ability to modulate intracellular processes involving coiled-coil structures.

Further, peptides of the invention include DP107 and DP178 are described herein having amino acid sequences recognized by the 107x178x4, ALLMOTI5, and PLZIP search motifs. Such motifs are also discussed.

Also described here are antifusogenic, antiviral, intracellular modulatory, and diagnostic uses of the peptides of the invention. Further, procedures are described for the use of the peptides of the invention for the identification of compounds exhibiting antifusogenic, antiviral or intracellular modulatory activity.

While not limited to any theory of operation, the following model is proposed to explain the potent anti-HIV activity of DP178, based, in part, on the experiments described in the Examples, infra. In the HIV protein, gp41, DP178 corresponds to a putative α-helix region located in the C-terminal end of the gp41 ectodomain, and appears to associate with a distal site on gp41 whose interactive structure is influenced

by the leucine zipper motif, a coiled-coil structure, referred to as DP107. The association of these two domains may reflect a molecular linkage or "molecular clasp" intimately involved in the fusion process. It is of interest that mutations in the C-terminal α-helix motif of gp41 (i.e., the D178 domain) tend to enhance the fusion ability of gp41, whereas mutations in the leucine zipper region (i.e., the DP107 domain) decrease or abolish the fusion ability of the viral protein. It may be that the leucine zipper motif is involved in membrane fusion while the C-terminal α-helix motif serves as a molecular safety to regulate the availability of the leucine zipper during virus-induced membrane fusion.

On the basis of the foregoing, two models are proposed of gp41-mediated membrane fusion which are schematically shown in FIG. 11A-B. The reason for proposing two models is that the temporal nature of the interaction between the regions defined by DP107 and DP178 cannot, as yet, be pinpointed. Each model envisions two conformations for gp41 - one in a "native" state as it might be found on a resting virion. The other in a "fusogenic" state to reflect conformational changes triggered following binding of gp120 to CD4 and just prior to fusion with the target cell membrane. The strong binding affinity between gp120 and CD4 may actually represent the trigger for the fusion process obviating the need for a pH change such as occurs for viruses that fuse within intracellular vesicles. The two major features of both models are: (1) the leucine zipper sequences (DP107) in each chain of oligomeric enveloped are held apart in the native state and are only allowed access

to one another in the fusogenic state so as to form the extremely stable coiled-coils, and (2) association of the DP178 and DP107 sites as they exist in gp41 occur either in the native or fusogenic state. FIG. 11A depicts DP178/DP107 interaction in the native state as a molecular clasp. On the other hand, if one assumes that the most stable form of the enveloped occurs in the fusogenic state, the model in FIG. 11B can be considered.

When synthesized as peptides, both DP107 and DP178 are potent inhibitors of HIV infection and fusion, probably by virtue of their ability to form complexes with viral gp41 and interfere with its fusogenic process; e.g., during the structural transition of the viral protein from the native structure to the fusogenic state, the DP178 and DP107 peptides may gain access to their respective binding sites on the viral gp41, and exert a disruptive influence. DP107 peptides which demonstrate anti-HIV activity are described in Applicants' co-pending application Serial No. 08/264,531, filed June 23, 1994, which is incorporated by reference herein in its entirety.

As shown in the Examples, infra, a truncated recombinant gp41 protein corresponding to the ectodomain of gp41 containing both DP107 and DP178 domains (excluding the fusion peptide, transmembrane region and cytoplasmic domain of gp41) did not inhibit HIV-1 induced fusion. However, when a single mutation was introduced to disrupt the coiled-coil structure of the DP107 domain -- a mutation which results in a total loss of biological activity of DP107 peptides -- the inactive recombinant protein was transformed to an

active inhibitor of HIV-1 induced fusion. This transformation may result from liberation of the potent DP178 domain from a molecular clasp with the leucine zipper, DP107 domain.

For clarity of discussion, the invention will be described primarily for DP178 peptide inhibitors of HIV. However, the principles may be analogously applied to other viruses, both enveloped and nonenveloped, and to other non-viral organisms.

5.1. DP178 AND DP178-LIKE PEPTIDES

The DP178 peptide (SEQ ID:1) of the invention corresponds to amino acid residues 638 to 673 of the transmembrane protein gp41 from the HIV-1_{LAI} isolate, and has the 36 amino acid sequence (reading from amino to carboxy terminus):

NH_2-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-COOH (SEQ ID:1)

In addition to the full-length DP178 (SEQ ID:1) 36-mer, the peptides of the invention may include truncations of the DP178 (SEQ ID:1) peptide which exhibit antifusogenic activity, antiviral activity and/or the ability to modulate intracellular processes involving coiled-coil peptide structures. Truncations of DP178 (SEQ ID:1) peptides may comprise peptides of between 3 and 36 amino acid residues (i.e., peptides ranging in size from a tripeptide to a 36-mer polypeptide), as shown in Tables I and IA, below. Peptide sequences in these tables are listed from amino (left) to carboxy (right) terminus. "X" may represent an amino group ($-NH_2$) and "Z" may represent a carboxyl (-COOH) group. Alternatively, "X" may represent a hydrophobic group, including but not limited to carbobenzyl, dansyl, or T-butoxycarbonyl; an acetyl group; a 9-fluorenylmethoxy-carbonyl (FMOC) group; or a covalently attached macromolecular group, including but not limited to a lipid-fatty acid conjugate, polyethylene glycol, carbohydrate or peptide group. Further, "Z" may represent an amido group; a T-butoxycarbonyl group; or a covalently attached macromolecular group, including but not limited to a lipid-fatty acid conjugate, polyethylene

glycol, carbohydrate or peptide group. A preferred "X" or "Z" macromolecular group is a peptide group.

TABLE I
DP178 (SEQ ID:1) CARBOXY TRUNCATIONS

X-YTS-Z
X-YTSL-Z
X-YTSLI-Z
X-YTSLIH-Z
X-YTSLIHS-Z
X-YTSLIHSL-Z
X-YTSLIHSLI-Z
X-YTSLIHSLIE-Z
X-YTSLIHSLIEE-Z
X-YTSLIHSLIEES-Z
X-YTSLIHSLIEESQ-Z
X-YTSLIHSLIEESQN-Z
X-YTSLIHSLIEESQNQ-Z
X-YTSLIHSLIEESQNQQ-Z
X-YTSLIHSLIEESQNQQE-Z
X-YTSLIHSLIEESQNQQEK-Z
X-YTSLIHSLIEESQNQQEKN-Z
X-YTSLIHSLIEESQNQQEKNE-Z
X-YTSLIHSLIEESQNQQEKNEQ-Z
X-YTSLIHSLIEESQNQQEKNEQE-Z
X-YTSLIHSLIEESQNQQEKNEQEL-Z
X-YTSLIHSLIEESQNQQEKNEQELL-Z
X-YTSLIHSLIEESQNQQEKNEQELLE-Z
X-YTSLIHSLIEESQNQQEKNEQELLEL-Z
X-YTSLIHSLIEESQNQQEKNEQELLELD-Z
X-YTSLIHSLIEESQNQQEKNEQELLELDK-Z
X-YTSLIHSLIEESQNQQEKNEQELLELDKW-Z
X-YTSLIHSLIEESQNQQEKNEQELLELDKWA-Z
X-YTSLIHSLIEESQNQQEKNEQELLELDKWAS-Z
X-YTSLIHSLIEESQNQQEKNEQELLELDKWASL-Z
X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLW-Z
X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWN-Z
X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNW-Z
X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z

The one letter amino acid code is used.

TABLE IA
DP178 (SEQ ID:1) AMINO TRUNCATIONS

X-NWF-Z
X-WNWF-Z
X-LWNWF-Z
X-SLWNWF-Z
X-ASLWNWF-Z
X-WASLWNWF-Z
X-KWASLWNWF-Z
X-DKWASLWNWF-Z
X-LDKWASLWNWF-Z
X-ELDKWASLWNWF-Z
X-LELDKWASLWNWF-Z
X-LLELDKWASLWNWF-Z
X-ELLELDKWASLWNWF-Z
X-QELLELDKWASLWNWF-Z
X-EQELLELDKWASLWNWF-Z
X-NEQELLELDKWASLWNWF-Z
X-KNEQELLELDKWASLWNWF-Z
X-EKNEQELLELDKWASLWNWF-Z
X-QEKNEQELLELDKWASLWNWF-Z
X-QQEKNEQELLELDKWASLWNWF-Z
X-NQQEKNEQELLELDKWASLWNWF-Z
X-QNQQEKNEQELLELDKWASLWNWF-Z
X-SQNQQEKNEQELLELDKWASLWNWF-Z
X-ESQNQQEKNEQELLELDKWASLWNWF-Z
X-EESQNQQEKNEQELLELDKWASLWNWF-Z
X-IEESQNQQEKNEQELLELDKWASLWNWF-Z
X-LIEESQNQQEKNEQELLELDKWASLWNWF-Z
X-SLIEESQNQQEKNEQELLELDKWASLWNWF-Z
X-HSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
X-IHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
X-LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
X-SLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
X-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z
X-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-Z

The one letter amino acid code is used.

The peptides of the invention also include DP178-like peptides. "DP178-like", as used herein, refers, first, to DP178 and DP178 truncations which contain one or more amino acid substitutions, insertions and/or deletions. Second, "DP-178-like" refers to peptide sequences identified or recognized by the ALLMOTI5, 107x178x4 and PLZIP search motifs described herein, having structural and/or amino acid motif similarity to DP178. The DP178-like peptides of the invention may exhibit antifusogenic or antiviral activity, or may exhibit the ability to modulate intracellular processes involving coiled-coil peptides. Further, such DP178-like peptides may possess additional advantageous features, such as, for example, increased bioavailability, and/or stability, or reduced host immune recognition.

HIV-1 and HIV-2 enveloped proteins are structurally distinct, but there exists a striking amino acid conservation within the DP178-corresponding regions of HIV-1 and HIV-2. The amino acid conservation is of a periodic nature, suggesting some conservation of structure and/or function. Therefore, one possible class of amino acid substitutions would include those amino acid changes which are predicted to stabilize the structure of the DP178 peptides of the invention. Utilizing the DP178 and DP178 analog sequences described herein, the skilled artisan can readily compile DP178 consensus sequences and ascertain from these, conserved amino acid residues which would represent preferred amino acid substitutions.

The amino acid substitutions may be of a conserved or non-conserved nature. Conserved amino acid substitutions consist of replacing one or more

amino acids of the DP178 (SEQ ID:1) peptide sequence with amino acids of similar charge, size, and/or hydrophobicity characteristics, such as, for example, a glutamic acid (E) to aspartic acid (D) amino acid substitution. Non-conserved substitutions consist of replacing one or more amino acids of the DP178 (SEQ ID:1) peptide sequence with amino acids possessing dissimilar charge, size, and/or hydrophobicity characteristics, such as, for example, a glutamic acid (E) to valine (V) substitution.

Amino acid insertions may consist of single amino acid residues or stretches of residues. The insertions may be made at the carboxy or amino terminal end of the DP178 or DP178 truncated peptides, as well as at a position internal to the peptide. Such insertions will generally range from 2 to 15 amino acids in length. It is contemplated that insertions made at either the carboxy or amino terminus of the peptide of interest may be of a broader size range, with about 2 to about 50 amino acids being preferred. One or more such insertions may be introduced into DP178 (SEQ.ID:1) or DP178 truncations, as long as such insertions result in peptides which may still be recognized by the 107x178x4, ALLMOTIS or PLZIP search motifs described herein, or may, alternatively, exhibit antifusogenic or antiviral activity, or exhibit the ability to modulate intracellular processes involving coiled-coil peptide structures.

Preferred amino or carboxy terminal insertions are peptides ranging from about 2 to about 50 amino acid residues in length, corresponding to gp41 protein regions either amino to or carboxy to the actual DP178 gp41 amino acid sequence, respectively. Thus, a

preferred amino terminal or carboxy terminal amino acid insertion would contain gp41 amino acid sequences found immediately amino to or carboxy to the DP178 region of the gp41 protein.

Deletions of DP178 (SEQ ID:1) or DP178 truncations are also within the scope of the invention. Such deletions consist of the removal of one or more amino acids from the DP178 or DP178-like peptide sequence, with the lower limit length of the resulting peptide sequence being 4 to 6 amino acids. Such deletions may involve a single contiguous or greater than one discrete portion of the peptide sequences. One or more such deletions may be introduced into DP178 (SEQ.ID:1) or DP178 truncations, as long as such deletions result in peptides which may still be recognized by the 107x178x4, ALLMOTIS or PLZIP search motifs described herein, or may, alternatively, exhibit antifusogenic or antiviral activity, or exhibit the ability to modulate intracellular processes involving coiled-coil peptide structures.

DP178 analogs are further described, below, in Section 5.3.

5.2. DP107 AND DP107-LIKE PEPTIDES

Further, the peptides of the invention include peptides having amino acid sequences corresponding to DP107 analogs. DP107 is a 38 amino acid peptide which exhibits potent antiviral activity, and corresponds to residues 558 to 595 of HIV-1_{LAI} transmembrane (TM) gp41 protein, as shown here:

NH_2-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVERYLKDQ-COOH

(SEQ ID:25)

In addition to the full-length DP107 (SEQ ID:25) 38-mer, the peptides of the invention may include truncations of the DP107 (SEQ ID:25) peptide which exhibit antifusogenic activity, antiviral activity and/or the ability to modulate intracellular processes involving coiled-coil peptide structures. Truncations of DP107 (SEQ ID:25) peptides may comprise peptides of between 3 and 38 amino acid residues (i.e., peptides ranging in size from a tripeptide to a 38-mer polypeptide), as shown in Tables II and IIA, below. Peptide sequences in these tables are listed from amino (left) to carboxy (right) terminus. "X" may represent an amino group ($-NH_2$) and "Z" may represent a carboxyl (-COOH) group. Alternatively, "X" may represent a hydrophobic group, including but not limited to carbobenzyl, dansyl, or T-butoxycarbonyl; an acetyl group; a 9-fluorenylmethoxy-carbonyl (FMOC) group; or a covalently attached macromolecular group, including but not limited to a lipid-fatty acid conjugate, polyethylene glycol, carbohydrate or peptide group. Further, "Z" may represent an amido group; a T-butoxycarbonyl group; or a covalently attached macromolecular group, including but not limited to a lipid-fatty acid conjugate, polyethylene glycol, carbohydrate or peptide group. A preferred "X" or "Z" macromolecular group is a peptide group.

TABLE II
DP107 (SEQ ID:25) CARBOXY TRUNCATIONS

X-NNL-Z
X-NNLL-Z
X-NNLLR-Z
X-NNLLRA-Z
X-NNLLRAI-Z
X-NNLLRAIE-Z
X-NNLLRAIEA-Z
X-NNLLRAIEAQ-Z
X-NNLLRAIEAQQ-Z
X-NNLLRAIEAQQH-Z
X-NNLLRAIEAQQHL-Z
X-NNLLRAIEAQQHLL-Z
X-NNLLRAIEAQQHLLQ-Z
X-NNLLRAIEAQQHLLQL-Z
X-NNLLRAIEAQQHLLQLT-Z
X-NNLLRAIEAQQHLLQLTV-Z
X-NNLLRAIEAQQHLLQLTVW-Z
X-NNLLRAIEAQQHLLQLTVWQ-Z
X-NNLLRAIEAQQHLLQLTVWQI-Z
X-NNLLRAIEAQQHLLQLTVWQIK-Z
X-NNLLRAIEAQQHLLQLTVWQIKQ-Z
X-NNLLRAIEAQQHLLQLTVWQIKQL-Z
X-NNLLRAIEAQQHLLQLTVWQIKQLQ-Z
X-NNLLRAIEAQQHLLQLTVWQIKQLQA-Z
X-NNLLRAIEAQQHLLQLTVWQIKQLQAR-Z
X-NNLLRAIEAQQHLLQLTVWQIKQLQARI-Z
X-NNLLRAIEAQQHLLQLTVWQIKQLQARIL-Z
X-NNLLRAIEAQQHLLQLTVWQIKQLQARILA-Z
X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAV-Z
X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVE-Z
X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVER-Z
X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVERY-Z
X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVERYL-Z
X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVERYLK-Z
X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVERYLKD-Z
X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVERYLKDQ-Z

The one letter amino acid code is used.

TABLE IIA
DP178 (SEQ ID:25) AMINO TRUNCATIONS

X-KDQ- Z
X-LKDQ- Z
X-YLKDQ- Z
X-RYLKDQ- Z
X-ERYLKDQ- Z
X-VERYLKDQ- Z
X-AVERYLKDQ- Z
X-LAVERYLKDQ- Z
X-ILAVERYLKDQ- Z
X-RILAVERYLKDQ- Z
X-ARILAVERYLKDQ- Z
X-QARILAVERYLKDQ- Z
X-LQARILAVERYLKDQ- Z
X-QLQARILAVERYLKDQ- Z
X-KQLQARILAVERYLKDQ- Z
X-IKQLQARILAVERYLKDQ- Z
X-QIKQLQARILAVERYLKDQ- Z
X-WQIKQLQARILAVERYLKDQ- Z
X-VWQIKQLQARILAVERYLKDQ- Z
X-TVWQIKQLQARILAVERYLKDQ- Z
X-LTVWQIKQLQARILAVERYLKDQ- Z
X-QLTVWQIKQLQARILAVERYLKDQ- Z
X-LQLTVWQIKQLQARILAVERYLKDQ- Z
X-LLQLTVWQIKQLQARILAVERYLKDQ- Z
X-HLLQLTVWQIKQLQARILAVERYLKDQ- Z
X-QHLLQLTVWQIKQLQARILAVERYLKDQ- Z
X-QQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
X-AQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
X-EAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
X-IEAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
X-AIEAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
X-RAIEAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
X-LRAIEAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
X-LLRAIEAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
X-NLLRAIEAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z
X-NNLLRAIEAQQHLLQLTVWQIKQLQARILAVERYLKDQ- Z

The one letter amino acid code is used.

The peptides of the invention also include DP107-like peptides. "DP107-like", as used herein, refers, first, to DP107 and DP107 truncations which contain one or more amino acid substitutions, insertions and/or deletions. Second, "DP-107-like" refers to peptide sequences identified or recognized by the ALLMOTI5, 107x178x4 and PLZIP search motifs described herein, having structural and/or amino acid motif similarity to DP107. The DP107-like peptides of the invention may exhibit antifusogenic or antiviral activity, or may exhibit the ability to modulate intracellular processes involving coiled-coil peptides. Further, such DP107-like peptides may possess additional advantageous features, such as, for example, increased bioavailability, and/or stability, or reduced host immune recognition.

HIV-1 and HIV-2 enveloped proteins are structurally distinct, but there exists a striking amino acid conservation within the DP107-corresponding regions of HIV-1 and HIV-2. The amino acid conservation is of a periodic nature, suggesting some conservation of structure and/or function. Therefore, one possible class of amino acid substitutions would include those amino acid changes which are predicted to stabilize the structure of the DP107 peptides of the invention. Utilizing the DP107 and DP107 analog sequences described herein, the skilled artisan can readily compile DP107 consensus sequences and ascertain from these, conserved amino acid residues which would represent preferred amino acid substitutions.

The amino acid substitutions may be of a conserved or non-conserved nature. Conserved amino acid substitutions consist of replacing one or more

amino acids of the DP107 (SEQ ID:25) peptide sequence with amino acids of similar charge, size, and/or hydrophobicity characteristics, such as, for example, a glutamic acid (E) to aspartic acid (D) amino acid substitution. Non-conserved substitutions consist of replacing one or more amino acids of the DP107 (SEQ ID:25) peptide sequence with amino acids possessing dissimilar charge, size, and/or hydrophobicity characteristics, such as, for example, a glutamic acid (E) to valine (V) substitution.

Amino acid insertions may consist of single amino acid residues or stretches of residues. The insertions may be made at the carboxy or amino terminal end of the DP107 or DP107 truncated peptides, as well as at a position internal to the peptide. Such insertions will generally range from 2 to 15 amino acids in length. It is contemplated that insertions made at either the carboxy or amino terminus of the peptide of interest may be of a broader size range, with about 2 to about 50 amino acids being preferred. One or more such insertions may be introduced into DP107 (SEQ.ID:25) or DP107 truncations, as long as such insertions result in peptides which may still be recognized by the 107x178x4, ALLMOTI5 or PLZIP search motifs described herein, or may, alternatively, exhibit antifusogenic or antiviral activity, or exhibit the ability to modulate intracellular processes involving coiled-coil peptide structures.

Preferred amino or carboxy terminal insertions are peptides ranging from about 2 to about 50 amino acid residues in length, corresponding to gp41 protein regions either amino to or carboxy to the actual DP107 gp41 amino acid sequence, respectively. Thus, a

preferred amino terminal or carboxy terminal amino acid insertion would contain gp41 amino acid sequences found immediately amino to or carboxy to the DP107 region of the gp41 protein.

Deletions of DP107 (SEQ ID:25) or DP178 truncations are also within the scope of the invention. Such deletions consist of the removal of one or more amino acids from the DP107 or DP107-like peptide sequence, with the lower limit length of the resulting peptide sequence being 4 to 6 amino acids. Such deletions may involve a single contiguous or greater than one discrete portion of the peptide sequences. One or more such deletions may be introduced into DP107 (SEQ.ID:25) or DP107 truncations, as long as such deletions result in peptides which may still be recognized by the 107x178x4, ALLMOTI5 or PLZIP search motifs described herein, or may, alternatively, exhibit antifusogenic or antiviral activity, or exhibit the ability to modulate intracellular processes involving coiled-coil peptide structures.

DP107 and DP107 truncations are more fully described in Applicants' co-pending U.S. Patent Application Ser. No. 08/374,666, filed January 27, 1995, and which is incorporated herein by reference in its entirety. DP107 analogs are further described, below, in Section 5.3.

5.3. DP107 and DP178 ANALOGS

Peptides corresponding to analogs of the DP178, DP178 truncations, DP107 and DP107 truncation sequences of the invention, described, above, in Sections 5.1 and 5.2 may be found in other viruses,

including, for example, non-HIV-1_{LAI} enveloped viruses, non-enveloped viruses and other non-viral organisms.

The term "analog", as used herein, refers to a peptide which is recognized or identified via the 107x178x4, ALLMOTI5 and/or PLZIP search strategies discussed below. Further, such peptides may exhibit antifusogenic capability, antiviral activity, or the ability to modulate intracellular processes involving coiled-coil structures.

Such DP178 and DP107 analogs may, for example, correspond to peptide sequences present in TM proteins of enveloped viruses and may, additionally correspond to peptide sequences present in non enveloped and non-viral organisms. Such peptides may exhibit antifusogenic activity, antiviral activity, most particularly antiviral activity which is specific to the virus in which their native sequences are found, or may exhibit an ability to modulate intracellular processes involving coiled-coil peptide structures.

DP178 analogs are peptides whose amino acid sequences are comprised of the amino acid sequences of peptide regions of, for example, other (i.e., other than HIV-1_{LAI}) viruses that correspond to the gp41 peptide region from which DP178 (SEQ ID:1) was derived. Such viruses may include, but are not limited to, other HIV-1 isolates and HIV-2 isolates. DP178 analogs derived from the corresponding gp41 peptide region of other (i.e., non HIV-1_{LAI}) HIV-1 isolates may include, for example, peptide sequences as shown below.

NH_2-YTNTIYTLLEESQNQQEKNEQELLELDKWASLWNWF-COOH

(DP-185; SEQ ID:3);

NH_2-YTGIIYNLLEESQNQQEKNEQELLELDKWANLWNWF-COOH(SEQ ID:4);

NH_2-YTSLIYSLLEKSQIQQEKNEQELLELDKWASLWNWF-COOH (SEQ ID:5).

SEQ ID:3 (DP-185), SEQ ID:4, and SEQ ID:5 are derived from HIV-1_{SF2}, HIV-1_{RF}, and HIV-1_{MN} isolates, respectively. Underlined amino acid residues refer to those residues that differ from the corresponding position in the DP178 (SEQ ID:1) peptide. One such DP178 analog, DP-185 (SEQ ID:3), is described in the Example presented in Section 6, below, where it is demonstrated that DP-185 (SEQ ID:3) exhibits antiviral activity. The DP178 analogs of the invention may also include truncations, as described above. Further, the analogs of the invention modifications such those described for DP178 analogs in Section 5.1., above. It is preferred that the DP178 analogs of the invention represent peptides whose amino acid sequences correspond to the DP178 region of the gp41 protein, it is also contemplated that the peptides of the invention may, additionally, include amino sequences, ranging from about 2 to about 50 amino acid residues in length, corresponding to gp41 protein regions either amino to or carboxy to the actual DP178 amino acid sequence.

Striking similarities, as shown in FIG. 1, exist within the regions of HIV-1 and HIV-2 isolates which correspond to the DP178 sequence. A DP178 analog derived from the HIV-2_{NIH2} isolate has the 36 amino acid sequence (reading from amino to carboxy terminus):

NH_2-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-COOH (SEQ ID:7)

Table III and Table IV show some possible truncations of the HIV-2_{NIHZ} DP178 analog, which may comprise peptides of between 3 and 36 amino acid residues (i.e., peptides ranging in size from a tripeptide to a 36-mer polypeptide). Peptide sequences in these tables are listed from amino (left) to carboxy (right) terminus. "X" may represent an amino group ($-NH_2$) and "Z" may represent a carboxyl (-COOH) group. Alternatively, "X" may represent a hydrophobic group, including but not limited to carbobenzyl, dansyl, or T-butoxycarbonyl; an acetyl group; a 9-fluorenylmethoxy-carbonyl (FMOC) group; or a covalently attached macromolecular group, including but not limited to a lipid-fatty acid conjugate, polyethylene glycol, carbohydrate or peptide group. Further, "Z" may represent an amido group; a T-butoxycarbonyl group; or a covalently attached macromolecular group, including but not limited to a lipid-fatty acid conjugate, polyethylene glycol, carbohydrate or peptide group. A preferred "X" or "Z" macromolecular group is a peptide group.

TABLE III

HIV-2_{NIH2} DP178 analog carboxy truncations.

X-LEA-Z
X-LEAN-Z
X-LEANI-Z
X-LEANIS-Z
X-LEANISQ-Z
X-LEANISQS-Z
X-LEANISQSL-Z
X-LEANISQSLE-Z
X-LEANISQSLEQ-Z
X-LEANISQSLEQA-Z
X-LEANISQSLEQAQ-Z
X-LEANISQSLEQAQI-Z
X-LEANISQSLEQAQIQ-Z
X-LEANISQSLEQAQIQQ-Z
X-LEANISQSLEQAQIQQE-Z
X-LEANISQSLEQAQIQQEK-Z
X-LEANISQSLEQAQIQQEKN-Z
X-LEANISQSLEQAQIQQEKNM-Z
X-LEANISQSLEQAQIQQEKNMY-Z
X-LEANISQSLEQAQIQQEKNMYE-Z
X-LEANISQSLEQAQIQQEKNMYEL-Z
X-LEANISQSLEQAQIQQEKNMYELQ-Z
X-LEANISQSLEQAQIQQEKNMYELQK-Z
X-LEANISQSLEQAQIQQEKNMYELQKL-Z
X-LEANISQSLEQAQIQQEKNMYELQKLN-Z
X-LEANISQSLEQAQIQQEKNMYELQKLNS-Z
X-LEANISQSLEQAQIQQEKNMYELQKLNSW-Z
X-LEANISQSLEQAQIQQEKNMYELQKLNSWD-Z
X-LEANISQSLEQAQIQQEKNMYELQKLNSWDV-Z
X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVF-Z
X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFT-Z
X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTN-Z
X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNW-Z
X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z

The one letter amino acid code is used.

TABLE IV

HIV-2_{NIHz} DP178 analog amino truncations.

X-NWL-Z
X-TNWL-Z
X-FTNWL-Z
X-VFTNWL-Z
X-DVFTNWL-Z
X-WDVFTNWL-Z
X-SWDVFTNWL-Z
X-NSWDVFTNWL-Z
X-LNSWDVFTNWL-Z
X-KLNSWDVFTNWL-Z
X-QKLNSWDVFTNWL-Z
X-LQKLNSWDVFTNWL-Z
X-ELQKLNSWDVFTNWL-Z
X-YELQKLNSWDVFTNWL-Z
X-MYELQKLNSWDVFTNWL-Z
X-NMYELQKLNSWDVFTNWL-Z
X-KNMYELQKLNSWDVFTNWL-Z
X-EKNMYELQKLNSWDVFTNWL-Z
X-QEKNMYELQKLNSWDVFTNWL-Z
X-QQEKNMYELQKLNSWDVFTNWL-Z
X-IQQEKNMYELQKLNSWDVFTNWL-Z
X-QIQQEKNMYELQKLNSWDVFTNWL-Z
X-AQIQQEKNMYELQKLNSWDVFTNWL-Z
X-QAQIQQEKNMYELQKLNSWDVFTNWL-Z
X-EQAQIQQEKNMYELQKLNSWDVFTNWL-Z
X-LEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
X-SLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
X-QSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
X-SQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
X-ISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
X-NISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
X-ANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
X-EANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z
X-LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-Z

The one letter amino acid code is used.

DP178 and DP107 analogs are recognized or identified, for example, by utilizing one or more of the 107x178x4, ALLMOTI5 or PLZIP computer-assisted search strategies described and demonstrated, below, in the Examples presented in Sections 9 through 16 and 19 through 25. The search strategy identifies additional peptide regions which are predicted to have structural and/or amino acid sequence features similar to those of DP107 and/or DP178.

The search strategies are described fully, below, in the Example presented in Section 9. While this search strategy is based, in part, on a primary amino acid motif deduced from DP107 and DP178, it is not based solely on searching for primary amino acid sequence homologies, as such protein sequence homologies exist within, but not between major groups of viruses. For example, primary amino acid sequence homology is high within the TM protein of different strains of HIV-1 or within the TM protein of different isolates of simian immunodeficiency virus (SIV). Primary amino acid sequence homology between HIV-1 and SIV, however, is low enough so as not to be useful. It is not possible, therefore, to find peptide regions similar to DP107 or DP178 within other viruses, or within non-viral organisms, whether structurally, or otherwise, based on primary sequence homology, alone.

Further, while it would be potentially useful to identify primary sequence arrangements of amino acids based on, for example, the physical chemical characteristics of different classes of amino acids rather than based on the specific amino acids themselves, such search strategies have, until now, proven inadequate. For example, a computer algorithm designed by Lupas et al. to identify coiled-coil

propensities of regions within proteins (Lupas, A., et al., 1991 Science 252:1162-1164) is inadequate for identifying protein regions analogous to DP107 or DP178.

Specifically, analysis of HIV-1 gp160 (containing both gp120 and gp41) using the Lupas algorithm does not identify the coiled-coil region within DP107. It does, however, identify a region within DP178 beginning eight amino acids N-terminal to the start of DP178 and ending eight amino acids from the C-terminus. The DP107 peptide has been shown experimentally to form a stable coiled coil. A search based on the Lupas search algorithm, therefore, would not have identified the DP107 coiled-coil region. Conversely, the Lupas algorithm identified the DP178 region as a potential coiled-coil motif. However, the peptide derived from the DP178 region failed to form a coiled coil in solution.

A possible explanation for the inability of the Lupas search algorithm to accurately identify coiled-coil sequences within the HIV-1 TM, is that the Lupas algorithm is based on the structure of coiled coils from proteins that are not structurally or functionally similar to the TM proteins of viruses, antiviral peptides (e.g. DP107 and DP178) of which are an object of this invention.

The computer search strategy of the invention, as demonstrated in the Examples presented below, in Sections 9 through 16 and 19 through 25, successfully identifies regions of proteins similar to DP107 or DP178. This search strategy was designed to be used with a commercially-available sequence database package, preferably PC/Gene.

A series of search motifs, the 107x178x4, ALLMOTIS and PLZIP motifs, were designed and engineered to range in stringency from strict to broad, as discussed in this Section and in Section 9, with 107x178x4 being preferred. The sequences identified via such search motifs, such as those listed in Tables V-XIV, below, potentially exhibit antifusogenic, such as antiviral, activity, may additionally be useful in the identification of antifusogenic, such as antiviral, compounds, and are intended to be within the scope of the invention.

Coiled-coiled sequences are thought to consist of heptad amino acid repeats. For ease of description, the amino acid positions within the heptad repeats are sometimes referred to as A through G, with the first position being A, the second B, etc. The motifs used to identify DP107-like and DP178-like sequences herein are designed to specifically search for and identify such heptad repeats. In the descriptions of each of the motifs described, below, amino acids enclosed by brackets , i.e., [], designate the only amino acid residues that are acceptable at the given position, while amino acids enclosed by braces, i.e., {}, designate the only amino acids which are unacceptable at the given heptad position. When a set of bracketed or braced amino acids is followed by a number in parentheses i.e., (), it refers to the number of subsequent amino acid positions for which the designated set of amino acids hold, e.g, a (2) means "for the next two heptad amino acid positions".

The ALLMOTI5 is written as follows:

{CDGHP}-{CFP}(2)-{CDGHP}-{CFP}(3)-
{CDGHP}-{CFP}(2)-{CDGHP}-{CFP}(3)-
{CDGHP}-{CFP}(2)-{CDGHP}-{CFP}(3)-
{CDGHP}-{CFP}(2)-{CDGHP}-{CFP}(3)-
{CDGHP}-{CFP}(2)-{CDGHP}-{CFP}(3)-

Translating this motif, it would read: "at the first (A) position of the heptad, any amino acid residue except C, D, G, H, or P is acceptable, at the next two (B,C) amino acid positions, any amino acid residue except C, F, or P is acceptable, at the fourth heptad position (D), any amino acid residue except C, D, G, H, or P is acceptable, at the next three (E, F, G) amino acid positions, any amino acid residue except C, F, or P is acceptable. This motif is designed to search for five consecutive heptad repeats (thus the repeat of the first line five times), meaning that it searches for 35-mer sized peptides. It may also be designed to search for 28-mers, by only repeating the initial motif four times. With respect to the ALLMOTI5 motif, a 35-mer search is preferred. Those viral (non-bacteriophage) sequences identified via such an ALLMOTI5 motif are listed in Table V in U.S. Patent Application No. 08/470,896 filed on June 6, 1995 which is incorporated herein by reference in its entirety. These viral sequences potentially exhibit antiviral activity, may be useful in the the identification of antiviral compounds, and are intended to be within the scope of the invention. In those instances wherein a single gene exhibits greater than one sequence recognized by the ALLMOTI5 search motif, the amino a cid residue numbers of these sequences are listed under "Area 2", Area 3", etc. This convention is used for each of the Tables listed, below, at the end of this Section.

The 107x178x4 motif is written as follows:

[EFIKLNQSTVWY]-{CFMP}(2)-[EFIKLNQSTVWY]-{CFMP}(3)-
[EFIKLNQSTVWY]-{CFMP}(2)-[EFIKLNQSTVWY]-{CFMP}(3)-
[EFIKLNQSTVWY]-{CFMP}(2)-[EFIKLNQSTVWY]-{CFMP}(3)-
[EFIKLNQSTVWY]-{CFMP}(2)-[EFIKLNQSTVWY]-{CFMP}(3)-

Translating this motif, it would read: "at the first (A) position of the heptad, only amino acid residue E, F, I, K, L, N, Q, S, T, V, W, or Y is acceptable, at the next two (B,C) amino acid positions, any amino acid residue except C, F, M or P is acceptable, at the fourth position (D), only amino acid residue E, F, I, K, L, N, Q, S, T, V, W, or Y is acceptable, at the next three (E, F, G) amino acid positions, any amino acid residue except C, F, M or P is acceptable. This motif is designed to search for four consecutive heptad repeats (thus the repeat of the first line four times), meaning that it searches for 28-mer sized peptides. It may also be designed to search for 35-mers, by repeating the initial motif five times. With respect to the 107x178x4 motif, a 28-mer search is preferred.

Those viral (non-bacteriophage) sequences identified via such a 107x178x4 motif are listed in Table VI in U.S. Patent Application No. 08/470,896 filed on June 6, 1995, which is incorporated herein, by reference, in its entirety. Those viral (non-bacteriophage) sequences listed in Table VII of U.S. Patent Application No. 08/470,896 (incorporated herein by reference in its entirety) are particularly preferred.

The 107x178x4 search motif was also utilized to identify non-viral procaryotic protein sequences, as listed in Table VIII in U.S. Patent Application No. 08/470,896 filed on June 6, 1995, which is incorporated herein, by reference, in its entirety.

Further, this search motif was used to reveal a number of human proteins. The results of this human protein 107x178x4 search is listed in Table IX in U.S. Patent Application No. 08/470,896 filed on June 6, 1995, which is incorporated herein, by reference, in its entirety. The sequences listed in Tables VIII and IX, therefore, reveal peptides which may be useful as antifusogenic compounds or in the identification of antifusogenic compounds, and are intended to be within the scope of the invention.

The PLZIP series of motifs are as listed in FIG. 19. These motifs are designed to identify leucine zipper coiled-coil like heptads wherein at least one proline residue is present at some predefined distance N-terminal to the repeat. These PLZIP motifs find regions of proteins with similarities to HIV-1 DP178 generally located just N-terminal to the transmembrane anchor. These motifs may be translated according to the same convention described above. Each line depicted in FIG. 19 represents a single, complete search motif. "X" in these motifs refers to any amino acid residue. In instances wherein a motif contains two numbers within parentheses, this refers to a variable number of amino acid residues. For example, X (1,12) is translated to "the next one to twelve amino acid residues, inclusive, may be any amino acid".

Tables X through XIV in U.S. Patent Application No. 08/470,896 filed on June 6, 1995 (which is incorporated herein, by reference, in its entirety), list sequences identified via searches conducted with such PLZIP motifs. Specifically, Table X lists viral sequences identified via PCTLZIP, P1CTLZIP and P2CTLZIP search motifs, Table XI lists viral sequences

identified via P3CTLZIP, P4CTLZIP, P5CTLZIP and P6CTLZIP search motifs, Table XII lsts viral sequences identified via P7CTLZIP, P8CTLZIP and P9CTLZIP search motifs, Table XIII lists viral sequences identified via P12LZIPC searches and Table XIV lists viral sequences identified via P23TLZIPC search motifs The viral sequences listed in these tables represent peptides which potentially exhibit antiviral activity, may be useful in the identification of antiviral compounds, and are intended to be within the scope of the invention.

The Examples presented in Sections 17, 18, 26 and 27 below, demonstrate that viral sequences identified via the motif searches described herein identify substantial antiviral characteristics. Specifically, the Example presented in Section 17 describes peptides with anti-respiratory syncytial virus activity, the Example presented in Section 18 describes peptides with anti-parainfluenza virus activity, the Example presented in Section 26 describes peptides with anti-measles virus activity and the Example presented in Section 27 describes peptides with anti-simian immunodeficiency virus activity.

The DP107 and DP178 analogs may, further, contain any of the additional groups described for DP178, above, in Section 5.1. For example, these peptides may include any of the additional amino-terminal groups as described above for "X" groups, and may also include any of the carboxy-terminal groups as described, above, for "Z" groups.

Additionally, truncations of the identified DP107 and DP178 peptides are among the peptides of the invention. Further, such DP107 and DP178 analogs and DP107/DP178 analog truncations may exhibit one or more

amino acid substitutions, insertion, and/or deletions. The DP178 analog amino acid substitutions, insertions and deletions, are as described, above, for DP178-like peptides in Section 5.1. The DP-107 analog amino acid substitutions, insertions and deletions are also as described, above, for DP107-like peptides in Section 5.2. Representative examples of such DP107/DP178 truncations are provided in Tables XV through XXII of U.S. Patent Application Serial No. 08/470,896 filed on June 6, 1995, which is incorporated herein by reference in its entirety.

Other exemplary DP178 and DP107 peptides and DP178-like and DP107-like peptides which are considered part of the present invention include the peptides described in U.S. Patent Application Serial No. 09/315,304 filed on May 4, 1999 which is incorporated by reference in its entirety. Such DP178 and DP107 peptides and DP178-like and DP107-like peptides include, *e.g.*, the peptides listed below in Table V.

Other DP178, DP107, DP178-like and DP107-like peptides include peptides described, *e.g.*, in U.S. Patent Application Serial No. 08/038,387 filed on March 29, 1993, now U.S. Patent No. 5,627,023; in U.S. Patent Application Serial No. 08/073,028 filed on June 7, 1993, now U.S. Patent No. 5,464,933; in U.S. Patent Application Serial No. 08/255,208 filed on June, 7, 1994; in U.S. Patent Application Serial No. 08/360,107 filed on December 20, 1994 and in U.S. Patent Application Serial No. 08/470,896 filed on June 6, 1995 each of which is incorporated herein by reference in its entirety.

TABLE V

T No.	Sequence
1	GIKQLQARILAVERYLKDQ
2	NNLLRAIEAQQHLLQLTVW
3	NEQELLELDKWASLWNWF
4	YTSLIHSLIEESQNQQEK
5	Ac-VWGIKQLQARILAVERYLKDQQLLGIWG-NH2
6	QHLLQLTVWGIKQLQARILAVERYLKDQ
7	LRAIEAQQHLLQLTVWGIKQLQARILAV
8	VQQQNNLLARIEAQQHLLQLTVWGIKQL
9	RQLLSGIVQQQNNLLRAIEAQQHLLQLT
10	MTLTVQARQLLSGIVQQQNNLLRAIEAQ
12	VVSLSNGVSVLTSKVLDLKNYIDKQLL
13	LLSTNKAVVSLSNGVSVLTSKVLDLKNY
15	Ac-VLHLEGEVNKIKSALLSTNKAVVSLSNG-NH2
19	Ac-LLSTNKAVVSLSNGVSVLTSKVLDLKNY-NH2
20	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
21	Ac-NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
22	Ac-IELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-NH2
23	Ac-IELSNIKENKCNGTDAKVKLIKQELDKY-NH2
24	Ac-ENKCNGTDAKVKLIKQELDKYKNAVTEL-NH2
25	Ac-DAKVKLIKQELDKYKNAVTELQLLMQST-NH2
26	Ac-CNGTDAKVKLIKQELDKYKNAVTELQLL-NH2
27	Ac-SNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLL-NH2
28	Ac-ASGVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGV-NH2
29	Ac-SGVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNG-NH2
30	Ac-VLHLEGEVNKIKSALLSTHKAVVSLSNGVSVLTSK-NH2
31	Ac-ARKLQRMKQLEDKVEELLSKNYHYLENEVARLKKLV-NH2
32	Ac-RMKQLEDKVEELLSKNYHYLENEVARLKKLVGER-NH2
33	Ac-VQQQNNLLRAIEAQQHLLQLTVWGIKQL-NH2
34	Ac-LRAIEAQQHLLQLTVWGIKQLQARILAV-NH2
35	Ac-QHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
36	Ac-RQLLSGIVQQQNNLLRAIEAQQHLLQLT-NH2
37	Ac-MTLTVQARQLLSGIVQQQNNLLRAIEAQ-NH2
38	Ac-AKQARSDIEKLKEAIRDTNKAVQSVQSS-NH2
39	Ac-AAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSS-NH2
40	Ac-AKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVA-NH2
41	Ac-GTIALGVATSAQITAAVALVEAKQARSD-NH2
42	Ac-ATSAQITAAVALVEAKQARSDIEKLKEA-NH2
43	Ac-AAVALVEAKQARSDIEKLKEAIRDTNKANH2
44	Ac-IEKLKEAIRDTNKAVQSVQSSIGNLIVA-NH2
45	Ac-IRDTNKAVQSVQSSIGNLIVAIKSVQDY-NH2
46	Ac-AVQSVQSSIGNLIVAIKSVQDYVNKEIV-NH2
47	Ac-QARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLARILAVERYLKDQ-NH2
48	Ac-QARQLLSGIVQQQNNLLRAIEAQQHLLQ-NH2
49	Ac-MTWMEMDREINNYTSLIGSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
50	Ac-WMEWDREINNYTSLIGSLIEESQNQQEKNEQELLE-NH2
51	Ac-INNYTSLIGSLIEESQNQQEKNEQELLE-NH2
52	Ac-INNYTSLIGSLIEESQNQQEKNEQELLELDKWASL-NH2
53	Ac-EWDREINNYTSLIGSLIEESQNQQEKNEQEGGC-NH2
54	Ac-QSRTLLAGIVQQQQQLLDVVKRQQELLR-NH2

T No.	Sequence
55	Ac-NNDTWQEWERKVDFLEENITALLEEAQIQQEKNMYELQKLNSWD-NH2
56	Ac-WQEWERKVDFLEENITALLEEAQIQQEK-NH2
57	Ac-VDFLEENITALLEEAQIQQEKNMYELQK-NH2
58	Ac-ITALLEEAQIQQEKNMYELQKLNSWDVF-NH2
59	Ac-SSESFTLLEQWNNWKLQLAEQWLEQINEKHYLEDIS-NH2
60	Ac-DKWASLWNWF-NH2
61	Ac-NEQELLELDKWASLWNWF-NH2
62	Ac-EKNEQELLELDKWASLWNWF-NH2
63	Ac-NQQEKNEQELLELDKWASLWNWF-NH2
64	Ac-ESQNQQEKNEQELLELDKWASLWNWF-NH2
65	Ac-LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
66	Ac-NDQKKLMSNNVQIVRQQSYSIMSIIKEE-NH2
67	Ac-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
68	Ac-VSKGYSALRTGWYTSVITIELSNIKEN-NH2
69	Ac-VVSLSNGVSVLTSKVLDLKNYIDKQLL-NH2
70	Ac-VNKIKSALLSTNKAVVSLSNGVSVLTSK-NH2
71	Ac-PIINFYDPLVFPSDEFDASISQVNEKINQSLAFIR-NH2
72	Ac-NLVYAQLQFTYDTLRGYINRALAQIAEA-NH2
73	Ac-LNQVDLTETLERYQQRLNTYALVSKDASYRS-NH2
74	Ac-ELLVLKKAQLNRHSYLKDSDFLDAALD-NH2
75	Ac-LAEAGEESVTEDTEREDTEEEREDEEE-NH2
76	Ac-ALLAEAGEESVTEDTEREDTEEEREDEEEENEART-NH2
77	Ac-ETERSVDLVAALLAEAGEESVTEDTEREDTEEERE-NH2
78	Ac-EESVTEDTEREDTEEEREDEEEENEART-NH2
79	Ac-VDLVAALLAEAGEESVTEDTEREDTEEE-NH2
80	Ac-NSETERSVDLVAALLAEAGEESVTE-NH2
81	Ac-DISYAQLQFTYDVLKDYINDALRNIMDA-NH2
82	Ac-SNVFSKDEIMREYNSQKQHIRTLSAKVNDN-NH2
83	Biotin-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
84	Dig-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
85	Biotin-NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
86	Dig-NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
87	Ac-VLHQLNIQLKQYLETQERLLAGNRIAARQLLQIWKDVA-NH2
88	Ac-LWHEQLLNTAQRAGLQLQLINQALAVREKVLIRYDIQK-NH2
89	Ac-LLDNFESTWEQSKELWEQQEISIQNLHKSALQEYW-NH2
90	Ac-LSNLLQISNNSDEWLEALEIEHEKWKLTQWQSYEQF-NH2
91	Ac-KLEALEGKLEALEGKLEALEGKLEALEGKLEALEGK-NH2
92	Ac-ELRALRGELRALRGELRALRGELRALRGK-NH2
93	Ac-ELKAKELEGEGLAEGEEALKGLLEKAAKLEGLELLK-NH2
94	Ac-WEAAAREAAAREAAAREAAARA-NH2
95	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNAF-NH2
96	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLANWF-NH2
97	Ac-YTSLIHSLIEESQNQQEKNQQELLELDKWASLWNWF-NH2
98	Ac-YTSLIHSLIEESQNQQEKNEQELLQLDKWASLWNWF-NH2
99	Ac-YTSLIHSLIEESQNQQEKNQQELLQLDKWASLWNWF-NH2
100	Ac-RMKQLEDKVEELLSKNYHLENEVARLKKLVGER-NH2
101	Ac-QQLLQLTVWGIKQLQARILAVERYLKNQ-NH2
102	Ac-NEQELLELDKWASLWNWF-NH2
103	Ac-YTSLIQSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
104	Ac-IINFYDPLVFPSDEFDASISQVNEKINQSLAFIRK-NH2

T No.	Sequence
105	Ac-INFYDPLVFPSDEFDASISQVNEKINQSLAFIRKS-NH2
106	Ac-NFYDPLVFPSDEFDASISQVNEKINQSLAFIRKSD-NH2
107	Ac-FYDPLVFPSDEFDASISQVNEKINQSLAFIRKSDE-NH2
108	Ac-YDPLVFPSDEFDASISQVNEKINQSLAFIRKSDEL-NH2
109	Ac-DPLVFPSDEFDASISQVNEKINQSLAFIRKSDELL-NH2
110	Ac-PLVFPSDEFDASISQVNEKINQSLAFIRKSDELLH-NH2
111	Ac-LVFPSDEFDASISQVNEKINQSLAFIRKSDELLHN-NH2
112	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
113	Ac-FPSDEFDASISQVNEKINQSLAFIRKSDELLHNVN-NH2
114	Ac-PSDEFDASISQVNEKINQSLAFIRKSDELLHNVNA-NH2
115	Ac-SDEFDASISQVNEKINQSLAFIRKSDELLHNVNAG-NH2
116	Ac-DEFDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2
117	Ac-EFDASISQVNEKINQSLAFIRKSDELLHNVNAGKS-NH2
118	Ac-FDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
119	Ac-DASISQVNEKINQSLAFIRKSDELLHNVNAGKSTT-NH2
120	Ac-ASGVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSN-NH2
121	Ac-SGVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNG-NH2
122	Ac-GVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGV-NH2
123	Ac-VAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVS-NH2
124	Ac-AVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSV-NH2
125	Ac-VSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVL-NH2
126	Ac-SKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLT-NH2
127	Ac-KVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTS-NH2
128	Ac-VLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSK-NH2
129	Ac-LHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKV-NH2
130	Ac-HLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVL-NH2
131	Ac-LEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLD-NH2
132	Ac-EGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDL-NH2
133	Ac-GEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLK-NH2
134	Ac-EVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKN-NH2
135	Ac-VNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNY-NH2
136	Ac-NKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYI-NH2
137	Ac-KIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYID-NH2
138	Ac-IKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDK-NH2
139	Ac-KSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQ-NH2
140	Ac-SALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQL-NH2
141	Ac-ALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLL-NH2
142	Ac-YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYK-NH2
143	Ac-TSVITIELSNIKENKCNGTDAKVKLIKQELDKYKN-NH2
144	Ac-SVITIELSNIKENKCNGTDAKVKLIKQELDKYKNA-NH2
145	Ac-VITIELSNIKENKCNGTDAKVKLIKQELDKYKNAV-NH2
146	Ac-ITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVT-NH2
147	Ac-TIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTE-NH2
148	Ac-IELSNIKENKCNGTDAKVKLIKQELDKYKNAVTEL-NH2
149	Ac-ELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQ-NH2
150	Ac-LSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQL-NH2
151	Ac-SNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLL-NH2
152	Ac-NIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLM-NH2
153	Ac-IKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQ-NH2
154	Ac-KENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQS-NH2

T No.	Sequence
155	Ac-ENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-NH2
156	Ac-LLDNFESTWEQSKELWELQEISIQNLHKSALQEYWN-NH2
157	Ac-ALGVATSAQITAAVALVEAKQARSDIEKLKEAIRD-NH2
158	Ac-LGVATSAQITAAVALVEAKQARSDIEKLKEAIRDT-NH2
159	Ac-GVATSAQITAAVALVEAKQARSDIEKLKEAIRDTN-NH2
160	Ac-VATSAQITAAVALVEAKQARSDIEKLKEAIRDTNK-NH2
161	Ac-ATSAQITAAVALVEAKQARSDIEKLKEAIRDTNKA-NH2
162	Ac-TSAQITAAVALVEAKQARSDIEKLKEAIRDTNKAV-NH2
163	Ac-SAQITAAVALVEAKQARSDIEKLKEAIRDTNKAVQ-NH2
164	Ac-AQITAAVALVEAKQARSDIEKLKEAIRDTNKAVQS-NH2
165	Ac-QITAAVALVEAKQARSDIEKLKEAIRDTNKAVQSV-NH2
166	Ac-ITAAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQ-NH2
167	Ac-TAAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQS-NH2
168	Ac-AAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSS-NH2
169	Ac-AVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSI-NH2
170	Ac-VALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIG-NH2
171	Ac-ALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGN-NH2
172	Ac-LVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNL-NH2
173	Ac-VEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLI-NH2
174	Ac-EAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIV-NH2
175	Ac-KQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAI-NH2
176	Ac-QARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIK-NH2
177	Ac-ARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKS-NH2
178	Ac-RSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSV-NH2
179	Ac-SDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQ-NH2
180	Ac-DIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQD-NH2
181	Ac-IEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDY-NH2
182	Ac-EKLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYV-NH2
183	Ac-KLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVN-NH2
184	Ac-LKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNK-NH2
185	Ac-KEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNKE-NH2
186	Ac-EAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNKEI-NH2
187	Ac-AIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNKEIV-NH2
188	Ac-IRDTNKAVQSVQSSIGNLIVAIKSVQDYVNKEIV-NH2
189	Ac-YTPNDITLNNSVALDPIDISIELNKAKSDLEESKE-NH2
190	Ac-TPNDITLNNSVALDPIDISIELNKAKSDLEESKEW-NH2
191	Ac-PNDITLNNSVALDPIDISIELNKAKSDLEESKEWI-NH2
192	Ac-NDITLNNSVALDPIDISIELNKAKSDLEESKEWIR-NH2
193	Ac-DITLNNSVALDPIDISIELNKAKSDLEESKEWIRR-NH2
194	Ac-ITLNNSVALDPIDISIELNKAKSDLEESKEWIRRS-NH2
195	Ac-TLNNSVALDPIDISIELNKAKSDLEESKEWIRRSN-NH2
196	Ac-LNNSVALDPIDISIELNKAKSDLEESKEWIRRSNQ-NH2
197	Ac-NNSVALDPIDISIELNKAKSDLEESKEWIRRSNQK-NH2
198	Ac-NSVALDPIDISIELNKAKSDLEESKEWIRRSNQKL-NH2
200	Ac-SVALDPIDISIELNKAKSDLEESKEWIRRSNQKLD-NH2
201	Ac-VALDPIDISIELNKAKSDLEESKEWIRRSNQKLDS-NH2
202	Ac-ALDPIDISIELNKAKSDLEESKEWIRRSNQKLDSI-NH2
203	Ac-LDPIDISIELNKAKSDLEESKEWIRRSNQKLDSIG-NH2
204	Ac-DPIDISIELNKAKSDLEESKEWIRRSNQKLDSIGN-NH2
205	Ac-PIDISIELNKAKSDLEESKEWIRRSNQKLDSIGNW-NH2

T No.	Sequence
206	Ac-IDISIELNKAKSDLEESKEWIRRSNQKLDSIGNWH-NH2
207	Ac-DISIELNKAKSDLEESKEWIRRSNQKLDSIGNWHQ-NH2
208	Ac-ISIELNKAKSDLEESKEWIRRSNQKLDSIGNWHQS-NH2
209	Ac-SIELNKAKSDLEESKEWIRRSNQKLDSIGNWHQSS-NH2
210	Ac-IELNKAKSDLEESKEWIRRSNQKLDSIGNWHQSST-NH2
211	Ac-ELNKAKSDLEESKEWIRRSNQKLDSIGNWHQSSTT-NH2
212	Ac-ELRALRGELRALRGELRALRGELRALRGELRALRGK-NH2
213	Ac-YTSLIHSLIEESQNQQQKNEQELLELDKWASLWNWF-NH2
214	Ac-YTSLIHSLIEESQNQQEKNEQELLELNKWASLWNWF-NH2
215	Ac-YTSLIHSLIEQSQNQQEKNEQELLELDKWASLWNWF-NH2
216	Ac-YTSLIHSLIQESQNQQEKNEQELLELDKWASLWNWF-NH2
217	Ac-YTSLIHSLIQQSQNQQQKNQQQLLQLNKWASLWNWF-NH2
218	Ac-EQELLELDKWASLWNWF-NH2
219	Ac-QELLELDKWASLWNWF-NH2
220	Ac-ELLELDKWASLWNWF-NH2
221	Ac-LELDKWASLWNWF-NH2
222	Ac-ELDKWASLWNWF-NH2
226	Ac-WASLWNWF-NH2
227	Ac-ASLWNWF-NH2
229	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLANAA-NH2
230	Ac-YTSLIHSLIEESQNQQEKNEQQLLELDKWASLWNWF-NH2
231	Ac-YTSLIQSLIEESQNQQEKNQQELLELDKWASLWNWF-NH2
234	Ac-EAAAREAAAREAAARLELDKWASLWNWF-NH2
236	Ac-PSLRDPISAEISIQALSYALGGDINKVLEKLGYSG-NH2
237	Ac-SLRDPISAEISIQALSYALGGDINKVLEKLGYSGG-NH2
238	Ac-LRDPISAEISIQALSYALGGDINKVLEKLGYSGGD-NH2
239	Ac-RDPISAEISIQALSYALGGDINKVLEKLGYSGGDL-NH2
240	Ac-DPISAEISIQALSYALGGDINKVLEKLGYSGGDLL-NH2
241	Ac-PISAEISIQALSYALGGDINKVLEKLGYSGGDLLG-NH2
242	Ac-ISAEISIQALSYALGGDINKVLEKLGYSGGDLLGI-NH2
243	Ac-SAEISIQALSYALGGDINKVLEKLGYSGGDLLGIL-NH2
244	Ac-AEISIQALSYALGGDINKVLEKLGYSGGDLLGILE-NH2
245	Ac-EISIQALSYALGGDINKVLEKLGYSGGDLLGILES-NH2
246	Ac-ISIQALSYALGGDINKVLEKLGYSGGDLLGILESR-NH2
247	Ac-SIQALSYALGGDINKVLEKLGYSGGDLLGILESRG-NH2
248	Ac-IQALSYALGGDINKVLEKLGYSGGDLLGILESRGI-NH2
249	Ac-QALSYALGGDINKVLEKLGYSGGDLLGILESRGIK-NH2
250	Ac-ALSYALGGDINKVLEKLGYSGGDLLGILESRGIKA-NH2
251	Ac-LSYALGGDINKVLEKLGYSGGDLLGILESRGIKAR-NH2
252	Ac-PDAVYLHRIDLGPPISLERLDVGTNLGNAIAKLED-NH2
253	Ac-DAVYLHRIDLGPPISLERLDVGTNLGNAIAKLEDA-NH2
254	Ac-AVYLHRIDLGPPISLERLDVGTNLGNAIAKLEDAK-NH2
255	Ac-VYLHRIDLGPPISLERLDVGTNLGNAIAKLEDAKE-NH2
256	Ac-YLHRIDLGPPISLERLDVGTNLGNAIAKLEDAKEL-NH2
257	Ac-LHRIDLGPPISLERLDVGTNLGNAIAKLEDAKELL-NH2
258	Ac-HRIDLGPPISLERLDVGTNLGNAIAKLEDAKELLE-NH2
259	Ac-RIDLGPPISLERLDVGTNLGNAIAKLEDAKELLES-NH2
260	Ac-IDLGPPISLERLDVGTNLGNAIAKLEDAKELLESS-NH2
261	Ac-DLGPPISLERLDVGTNLGNAIAKLEDAKELLESSD-NH2
262	Ac-LGPPISLERLDVGTNLGNAIAKLEDAKELLESSDQ-NH2

T No.	Sequence
263	Ac-GPPISLERLDVGTNLGNAIAKLEDAKELLESSDQI-NH2
264	Ac-PPISLERLDVGTNLGNAIAKLEDAKELLESSDQIL-NH2
265	Ac-PISLERLDVGTNLGNAIAKLEDAKELLESSDQILR-NH2
266	Ac-ISLERLDVGTNLGNAIAKLEDAKELLESSDQIRS-NH2
267	Ac-SLERLDVGTNLGNAIAKLEDAKELLESSDQILRSM-NH2
268	Ac-LERLDVGTNLGNAIAKLEDAKELLESSDQILRSMK-NH2
269	Ac-EWIRRSNQKLDSI-NH2
270	Ac-LELDKWASLANAF-NH2
271	Ac-LELDKWASLFNFF-NH2
272	Ac-LELDKWASLANWF-NH2
273	Ac-LELDKWASLWNAF-NH2
274	Ac-ELGNVNNSISNALDKLEESNSKLDKVNVKLTSTSA-NH2
275	Ac-TELGNVNNSISNALDKLEESNSKLDKVNVKLTSTS-NH2
276	Ac-STELGNVNNSISNALDKLEESNSKLDKVNVKLTST-NH2
277	Ac-ISTELGNVNNSISNALDKLEESNSKLDKVNVKLTS-NH2
278	Ac-DISTELGNVNNSISNALDKLEESNSKLDKVNVKLT-NH2
279	Ac-LDISTELGNVNNSISNALDKLEESNSKLDKVNVKL-NH2
280	Ac-NLDISTELGNVNNSISNALDKLEESNSKLDKVNVK-NH2
281	Ac-GNLDISTELGNVNNSISNALDKLEESNSKLDKVNV-NH2
282	Ac-TGNLDISTELGNVNNSISNALDKLEESNSKLDKVN-NH2
283	Ac-VTGNLDISTELGNVNNSISNALDKLEESNSKLDKV-NH2
284	Ac-IVTGNLDISTELGNVNNSISNALDKLEESNSKLDK-NH2
285	Ac-VIVTGNLDISTELGNVNNSISNALDKLEESNSKLD-NH2
286	Ac-QVIVTGNLDISTELGNVNNSISNALDKLEESNSKL-NH2
287	Ac-SQVIVTGNLDISTELGNVNNSISNALDKLEESNSK-NH2
288	Ac-DSQVIVTGNLDISTELGNVNNSISNALDKLEESNS-NH2
289	Ac-LDSQVIVTGNLDISTELGNVNNSISNALDKLEESN-NH2
290	Ac-ILDSQVIVTGNLDISTELGNVNNSISNALDKLEES-NH2
291	Ac-SILDSQVIVTGNLDISTELGNVNNSISNALDKLEE-NH2
292	Ac-ISILDSQVIVTGNLDISTELGNVNNSISNALDKLE-NH2
293	Ac-NISILDSQVIVTGNLDISTELGNVNNSISNALDKL-NH2
294	Ac-KNISILDSQVIVTGNLDISTELGNVNNSISNALDK-NH2
295	Ac-QKNISILDSQVIVTGNLDISTELGNVNNSISNALD-NH2
296	Ac-YQKNISILDSQVIVTGNLDISTELGNVNNSISNAL-NH2
297	Ac-TYQKNISILDSQVIVTGNLDISTELGNVNNSISNA-NH2
298	Ac-ATYQKNISILDSQVIVTGNLDISTELGNVNNSISN-NH2
299	Ac-DATYQKNISILDSQVIVTGNLDISTELGNVNNSIS-NH2
300	Ac-FDATYQKNISILDSQVIVTGNLDISTELGNVNNSI-NH2
301	Ac-EFDATYQKNISILDSQVIVTGNLDISTELGNVNNS-NH2
302	Ac-GEFDATYQKNISILDSQVIVTGNLDISTELGNVNN-NH2
303	Ac-SGEFDATYQKNISILDSQVIVTGNLDISTELGNVN-NH2
304	Ac-LSGEFDATYQKNISILDSQVIVTGNLDISTELGNV-NH2
305	Ac-RLSGEFDATYQKNISILDSQVIVTGNLDISTELGN-NH2
306	Ac-LRLSGEFDATYQKNISILDSQVIVTGNLDISTELG-NH2
307	Ac-TLRLSGEFDATYQKNISILDSQVIVTGNLDISTEL-NH2
308	Ac-ITLRLSGEFDATYQKNISILDSQVIVTGNLDISTE-NH2
309	Ac-GITLRLSGEFDATYQKNISILDSQVIVTGNLDIST-NH2
310	Ac-TATIEAVHEVTDGLSQLAVAVGKMQQFVNDQFNNT-NH2
311	Ac-ITATIEAVHEVTDGLSQLAVAVGKMQQFVNDQFNN-NH2
312	Ac-SITATIEAVHEVTDGLSQLAVAVGKMQQFVNDQFN-NH2

T No.	Sequence
314	Ac-KESITATIEAVHEVTDGLSQLAVAVGKMQQFVNDQ-NH2
315	Ac-LKESITATIEAVHEVTDGLSQLAVAVGKMQQFVND-NH2
316	Ac-RLKESITATIEAVHEVTDGLSQLAVAVGKMQQFVN-NH2
317	Ac-LRLKESITATIEAVHEVTDGLSQLAVAVGKMQQFV-NH2
318	Ac-ILRLKESITATIEAVHEVTDGLSQLAVAVGKMQQF-NH2
319	Ac-NILRLKESITATIEAVHEVTDGLSQLAVAVGKMQQ-NH2
320	Ac-ANILRLKESITATIEAVHEVTDGLSQLAVAVGKMQ-NH2
321	Ac-AANILRLKESITATIEAVHEVTDGLSQLAVAVGKM-NH2
322	Ac-HKCDDECMNSVKNGTYDYPKYEEESKLNRNEIKGV-NH2
323	Ac-KCDDECMNSVKNGTYDYPKYEEESKLNRNEIKGVK-NH2
324	Ac-CDDECMNSVKNGTYDYPKYEEESKLNRNEIKGVKL-NH2
325	Ac-DDECMNSVKNGTYDYPKYEEESKLNRNEIKGVKLS-NH2
326	Ac-DECMNSVKNGTYDYPKYEEESKLNRNEIKGVKLSS-NH2
327	Ac-ECMNSVKNGTYDYPKYEEESKLNRNEIKGVKLSSM-NH2
328	Ac-CMNSVKNGTYDYPKYEEESKLNRNEIKGVKLSSMG-NH2
329	Ac-MNSVKNGTYDYPKYEEESKLNRNEIKGVKLSSMGV-NH2
330	Ac-NSVKNGTYDYPKYEEESKLNRNEIKGVKLSSMGVY-NH2
331	Ac-SVKNGTYDYPKYEEESKLNRNEIKGVKLSSMGVYQ-NH2
332	Ac-VKNGTYDYPKYEEESKLNRNEIKGVKLSSMGVYQI-NH2
333	Ac-KNGTYDYPKYEEESKLNRNEIKGVKLSSMGVYQIL-NH2
334	Ac-AFIRKSDELLHNV-NH2
335	Ac-VVLAGAALGVATAAQITAGIALHQSMLNSQAIDNL-NH2
336	Ac-VLAGAALGVATAAQITAGIALHQSMLNSQAIDNLR-NH2
337	Ac-LAGAALGVATAAQITAGIALHQSMLNSQAIDNLRA-NH2
338	Ac-AGAALGVATAAQITAGIALHQSMLNSQAIDNLRAS-NH2
339	Ac-GAALGVATAAQITAGIALHQSMLNSQAIDNLRASL-NH2
340	Ac-AALGVATAAQITAGIALHQSMLNSQAIDNLRASLE-NH2
341	Ac-ALGVATAAQITAGIALHQSMLNSQAIDNLRASLET-NH2
342	Ac-LGVATAAQITAGIALHQSMLNSQAIDNLRASLETT-NH2
343	Ac-GVATAAQITAGIALHQSMLNSQAIDNLRASLETTN-NH2
344	Ac-VATAAQITAGIALHQSMLNSQAIDNLRASLETTNQ-NH2
345	Ac-ATAAQITAGIALHQSMLNSQAIDNLRASLETTNQA-NH2
346	Ac-TAAQITAGIALHQSMLNSQAIDNLRASLETTNQAI-NH2
347	Ac-AAQITAGIALHQSMLNSQAIDNLRASLETTNQAIE-NH2
348	Ac-AQITAGIALHQSMLNSQAIDNLRASLETTNQAIEA-NH2
349	Ac-QITAGIALHQSMLNSQAIDNLRASLETTNQAIEAI-NH2
350	Ac-ITAGIALHQSMLNSQAIDNLRASLETTNQAIEAIR-NH2
351	Ac-TAGIALHQSMLNSQAIDNLRASLETTNQAIEAIRQ-NH2
352	Ac-AGIALHQSMLNSQAIDNLRASLETTNQAIEAIRQA-NH2
353	Ac-GIALHQSMLNSQAIDNLRASLETTNQAIEAIRQAG-NH2
354	Ac-IALHQSMLNSQAIDNLRASLETTNQAIEAIRQAGQ-NH2
355	Ac-ALHQSMLNSQAIDNLRASLETTNQAIEAIRQAGQE-NH2
356	Ac-LHQSMLNSQAIDNLRASLETTNQAIEAIRQAGQEM-NH2
357	Ac-HQSMLNSQAIDNLRASLETTNQAIEAIRQAGQEMI-NH2
358	Ac-QSMLNSQAIDNLRASLETTNQAIEAIRQAGQEMIL-NH2
359	Ac-SMLNSQAIDNLRASLETTNQAIEAIRQAGQEMILA-NH2
360	Ac-MLNSQAIDNLRASLETTNQAIEAIRQAGQEMILAV-NH2
361	Ac-LNSQAIDNLRASLETTNQAIEAIRQAGQEMILAVQ-NH2
362	Ac-NSQAIDNLRASLETTNQAIEAIRQAGQEMILAVQG-NH2
363	Ac-SQAIDNLRASLETTNQAIEAIRQAGQEMILAVQGV-NH2

T No.	Sequence
364	Ac-QAIDNLRASLETTNQAIEAIRQAGQEMILAVQGVQ-NH2
365	Ac-AIDNLRASLETTNQAIEAIRQAGQEMILAVQGVQD-NH2
366	Ac-IDNLRASLETTNQAIEAIRQAGQEMILAVQGVQDY-NH2
367	Ac-DNLRASLETTNQAIEAIRQAGQEMILAVQGVQDYI-NH2
368	Ac-NLRASLETTNQAIEAIRQAGQEMILAVQGVQDYIN-NH2
369	Ac-LRASLETTNQAIEAIRQAGQEMILAVQGVQDYINN-NH2
370	Ac-RASLETTNQAIEAIRQAGQEMILAVQGVQDYINNE-NH2
371	Ac-YTSVITIELSNIKENKUNGTDAVKLIKQELDKYK-NH2
372	Ac-TSVITIELSNIKENKUNGTDAVKLIKQELDKYKN-NH2
373	Ac-SVITIELSNIKENKUNGTDAVKLIKQELDKYKNA-NH2
374	Ac-SNIKENKUNGTDAKVKLIKQELDKYKNAVTELQLL-NH2
375	Ac-KENKUNGTDAKVKLIKQELDKYKNAVTELQLLMQS-NH2
376	Ac-CLELDKWASLWNWFC-NH2
377	Ac-CLELDKWASLANWFC-NH2
378	Ac-CLELDKWASLFNFFC-NH2
379	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLFNFF-NH2
381	Ac-RMKQLEDKVEELLSKNYHLENELELDKWASLWNWF-NH2
382	Ac-KVEELLSKNYHLENELELDKWASLWNWF-NH2
383	Ac-RMKQLEDKVEELLSKLEWIRRSNQKLDSI-NH2
384	Ac-RMKQLEDKVEELLSKLAFIRKSDELLHNV-NH2
385	Ac-ELEALRGELRALRGELELDKWASLWNWF-NH2
386	Ac-LDPIDISIELNKAKSDLEESKEWIRRSNQKLDSI-NH2
387	Ac-CNEQLSDSFPVEFFQV-NH2
388	Ac-MAEDDPYLGRPEQMFHLDPSL-NH2
389	Ac-EDFSSIADMDFSALLSQISS-NH2
390	Ac-TWQEWERKVDFLEENITALLEEAQIQQEKNMYELQ-NH2
391	Ac-WQEWERKVDFLEENITALLEEAQIQQEKNMYELQK-NH2
392	Ac-QEWERKVDFLEENITALLEEAQIQQEKNMYELQKL-NH2
393	Ac-EWERKVDFLEENITALLEEAQIQQEKNMYELQKLN-NH2
394	Ac-WERKVDFLEENITALLEEAQIQQEKNMYELQKLNS-NH2
395	Ac-ERKVDFLEENITALLEEAQIQQEKNMYELQKLNSW-NH2
396	Ac-RKVDFLEENITALLEEAQIQQEKNMYELQKLNSWD-NH2
397	Ac-KVDFLEENITALLEEAQIQQEKNMYELQKLNSWDV-NH2
398	Ac-VDFLEENITALLEEAQIQQEKNMYELQKLNSWDVF-NH2
399	Ac-DFLEENITALLEEAQIQQEKNMYELQKLNSWDVFG-NH2
400	Ac-FLEENITALLEEAQIQQEKNMYELQKLNSWDVFGN-NH2
401	Ac-LEENITALLEEAQIQQEKNMYELQKLNSWDVFGNW-NH2
402	Ac-LEENITALLEEAQIQQEKNMYELQKLNSWDVFGNWF-NH2
403	Ac-NEQSEEKENELYWAKEQLLDLLFNIFNQTVGAWIMQ-NH2
405	Ac-QQQLLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKD-NH2
406	Ac-QQLLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKDQ-NH2
407	Ac-QQLLDVVKRQQELLRLTVWGPKNLQTRVTAIEKYLKDQ-NH2
408	Ac-DERKQDKVLVVQQTGTLQLTLIQLEKTAKLQWVRLNRY-NH2
409	Ac-QQQLLDVVKRQQELLRLTVWGTKNLQTRVTAIEKY-NH2
410	Ac-QQLLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYL-NH2
411	Ac-QLLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLK-NH2
412	Ac-LLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKD-NH2
413	Ac-LDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKDQ-NH2
414	Ac-DVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKDQA-NH2
415	Ac-VVKRQQELLRLTVWGTKNLQTRVTAIEKYLKDQAQ-NH2

T No.	Sequence
416	Ac-VKRQQELLRLTVWGTKNLQTRVTAIEKYLKDQAQL-NH2
417	Ac-KRQQELLRLTVWGTKNLQTRVTAIEKYLKDQAQLN-NH2
418	Ac-RQQELLRLTVWGTKNLQTRVTAIEKYLKDQAQLNA-NH2
419	Ac-QQELLRLTVWGTKNLQTRVTAIEKYLKDQAQLNAW-NH2
420	Ac-QELLRLTVWGTKNLQTRVTAIEKYLKDQAQLNAWG-NH2
421	Ac-ELLRLTVWGTKNLQTRVTAIEKYLKDQAQLNAWGC-NH2
422	Ac-NNLLRAIEAQQHLLQLTVWGPKQLQARILAVERYLKDQ-NH2
423	Ac-SELEIKRYKNRVASRKCRAKFKQLLQHYREVAAAK-NH2
424	Ac-ELEIKRYKNRVASRKCRAKFKQLLQHYREVAAAKS-NH2
425	Ac-LEIKRYKNRVASRKCRAKFKQLLQHYREVAAAKSS-NH2
426	Ac-EIKRYKNRVASRKCRAKFKQLLQHYREVAAAKSSE-NH2
427	Ac-IKRYKNRVASRKCRAKFKQLLQHYREVAAAKSSEN-NH2
428	Ac-KRYKNRVASRKCRAKFKQLLQHYREVAAAKSSEND-NH2
429	Ac-RYKNRVASRKCRAKFKQLLQHYREVAAAKSSENDR-NH2
430	Ac-YKNRVASRKCRAKFKQLLQHYREVAAAKSSENDRL-NH2
431	Ac-KNRVASRKCRAKFKQLLQHYREVAAAKSSENDRLR-NH2
432	Ac-NRVASRKCRAKFKQLLQHYREVAAAKSSENDRLRL-NH2
433	Ac-RVASRKCRAKFKQLLQHYREVAAAKSSENDRLRLL-NH2
434	Ac-VASRKCRAKFKQLLQHYREVAAAKSSENDRLRLLL-NH2
435	Ac-ASRKCRAKFKQLLQHYREVAAAKSSENDRLRLLLK-NH2
436	Ac-SRKCRAKFKQLLQHYREVAAAKSSENDRLRLLLKQ-NH2
437	Ac-RKCRAKFKQLLQHYREVAAAKSSENDRLRLLLKQM-NH2
438	Ac-KCRAKFKQLLQHYREVAAAKSSENDRLRLLLKQMC-NH2
439	Ac-CRAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCP-NH2
440	Ac-RAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPS-NH2
441	Ac-AKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSL-NH2
442	Ac-KFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLD-NH2
443	Ac-FKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDV-NH2
444	Ac-KQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVD-NH2
445	Ac-QLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDS-NH2
446	Ac-LLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDSI-NH2
447	Ac-LQHYREVAAAKSSENDRLRLLLKQMCPSLDVDSII-NH2
448	Ac-QHYREVAAAKSSENDRLRLLLKQMCPSLDVDSIIP-NH2
449	Ac-HYREVAAAKSSENDRLRLLLKQMCPSLDVDSIIPR-NH2
450	Ac-YREVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRT-NH2
451	Ac-REVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTP-NH2
452	Ac-EVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTPD-NH2
453	Ac-VAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTPDV-NH2
454	Ac-AAAKSSENDRLRLLLKQMCPSLDVDSIIPRTPDVL-NH2
455	Ac-AAKSSENDRLRLLLKQMCPSLDVDSIIPRTPDVLH-NH2
456	Ac-AKSSENDRLRLLLKQMCPSLDVDSIIPRTPDVLHE-NH2
457	Ac-KSSENDRLRLLLKQMCPSLDVDSIIPRTPDVLHED-NH2
458	Ac-SSENDRLRLLLKQMCPSLDVDSIIPRTPDVLHEDL-NH2
459	Ac-SENDRLRLLLKQMCPSLDVDSIIPRTPDVLHEDLL-NH2
460	Ac-ENDRLRLLLKQMCPSLDVDSIIPRTPDVLHEDLLN-NH2
461	Ac-NDRLRLLLKQMCPSLDVDSIIPRTPDVLHEDLLNF-NH2
534	Ac-PGYRWMCLRRFIIFLFILLLCLIFLLVLLDYQGML-NH2
535	Ac-GYRWMCLRRFIIFLFILLLCLIFLLVLLDYQGMLP-NH2
536	Ac-YRWMCLRRFIIFLFILLLCLIFLLVLLDYQGMLPV-NH2
537	Ac-RWMCLRRFIIFLFILLLCLIFLLVLLDYQGMLPVC-NH2

T No.	Sequence
538	Ac-WMCLRRFIIFLFILLLCLIFLLVLLDYQGMLPVCP-NH2
539	Ac-MCLRRFIIFLFILLLCLIFLLVLLDYQGMLPVCPL-NH2
540	Ac-CLRRFIIFLFILLLCLIFLLVLLDYQGMLPVCPLI-NH2
541	Ac-LRRFIIFLFILLLCLIFLLVLLDYQGMLPVCPLIP-NH2
542	Ac-RRFIIFLFILLLCLIFLLVLLDYQGMLPVCPLIPG-NH2
543	Ac-RFIIFLFILLLCLIFLLVLLDYQGMLPVCPLIPGS-NH2
544	Ac-FIIFLFILLLCLIFLLVLLDYQGMLPVCPLIPGSS-NH2
545	Ac-IIFLFILLLCLIFLLVLLDYQGMLPVCPLIPGSST-NH2
546	Ac-IFLFILLLCLIFLLVLLDYQGMLPVCPLIPGSSTT-NH2
547	Ac-FLFILLLCLIFLLVLLDYQGMLPVCPLIPGSSTTS-NH2
548	Ac-LFILLLCLIFLLVLLDYQGMLPVCPLIPGSSTTST-NH2
549	Ac-FILLLCLIFLLVLLDYQGMLPVCPLIPGSSTTSTG-NH2
550	Ac-ILLLCLIFLLVLLDYQGMLPVCPLIPGSSTTSTGP-NH2
551	Ac-LLLCLIFLLVLLDYQGMLPVCPLIPGSSTTSTGPC-NH2
552	Ac-LLCLIFLLVLLDYQGMLPVCPLIPGSSTTSTGPCR-NH2
553	Ac-LCLIFLLVLLDYQGMLPVCPLIPGSSTTSTGPCRT-NH2
554	Ac-CLIFLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTC-NH2
555	Ac-LIFLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTCM-NH2
556	Ac-IFLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTCMT-NH2
557	Ac-FLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTCMTT-NH2
558	Ac-PPLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGT-NH2
559	Ac-LLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTT-NH2
560	Ac-LVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTV-NH2
561	Ac-VLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVC-NH2
562	Ac-LQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCL-NH2
563	Ac-QAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLG-NH2
564	Ac-AGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQ-NH2
565	Ac-GFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQN-NH2
566	Ac-FFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNS-NH2
567	Ac-FLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQ-NH2
568	Ac-LLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQS-NH2
569	Ac-LTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQSP-NH2
570	Ac-FWNWLSAWKDLELKSLLEEVKDELQKMR-NH2
571	Ac-NNLLRAIEAQQHLLQLTVW-NH2
572	Ac-CGGNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
573	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
574	C13H27CO-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
575	Ac-AVSKGYLSALRTGWYTSVITIELSNIKENKUNGTDA-NH2
576	Ac-SISNIETVIEFQQKNNRLLEITREFSVNAGVTTPVS-NH2
577	Ac-DQQIKQYKRLLDRLIIPLYDGLRQKDVIVSNQESN-NH2
578	Ac-YSELTNIFGDNIGSLQEKGIKLQGIASLYRTNITEI-NH2
579	Ac-TSITLQVRLPLLTRLLNTQIYRVDSISYNIQNREWY-NH2
580	Ac-VEIAEYRRLLRTVLEPIRDALNAMTQNIRPVQSVA-NH2
581	Ac-SYFIVLSIAYPTLSEIKGVIVHRLEGVSYNIGSQEW-NH2
582	Ac-LKEAIRDTNKAVQSVQSSIGNLIVAIKS-NH2
583	NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
583	NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
584	QKQEPIDKELYPLTSL
585	YPKFVKQNTLKLAT
586	QYIKANQKFIGITE

T No.	Sequence
587	NGQIGNDPNRDILY
588	AC-RPDVY-OH
589	CLELDKWASLWNWFC-(cyclic)
590	CLELDKWASLANWFC-(cyclic)
591	CLELDKWASLANFFC-(cyclic)
594	Ac-NNLLRAIEAQQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
595	Ac-CGGYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNNWF-NH2
596	Ac-PLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGT-NH2
597	Ac-LLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTT-NH2
598	Ac-LVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTV-NH2
599	Ac-VLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVC-NH2
600	Ac-LQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCL-NH2
601	Ac-QAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLG-NH2
602	Ac-AGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQ-NH2
603	Ac-GFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQN-NH2
604	Ac-FFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNS-NH2
605	Ac-FLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQ-NH2
606	Ac-LLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQS-NH2
607	Ac-LTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQSP-NH2
608	Ac-LELDKWASLWNWA-NH2
609	Ac-LELDKWASAWNWF-NH2
610	Ac-LELDKAASLWNWF-NH2
611	Ac-LKLDKWASLWNWF-NH2
612	Ac-LELKKWASLWNWF-NH2
613	Ac-DELLHNVNAGKST-NH2
614	Ac-KSDELLHNVNAGKST-NH2
615	Ac-IRKSDELLHNVNAGKST-NH2
616	Ac-AFIRKSDELLHNVNAGKST-NH2
617	Ac-FDASISQVNEKINQSLAFI-NH2
618	Ac-YAADKESTQKAFDGITNKVNSVIEKMNTQFEAVGKE-NH2
619	Ac-SVIEKMNTQFEAVGKEFGNLERRLENLNKRMEDGFL-NH2
620	Ac-VWTYNAELLVLMENERTLDFHDSNVKNLYDKVRMQL-NH2
621	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEGGC-NH2
622	Ac-INNYTSLIHSLIEESQNQQEKNEQELLELDKWASL-NH2
623	Ac-INNYTSLIHSLIEESQNQQEKNEQELLE-NH2
624	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLE-NH2
625	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
626	Ac-IDISIELNKAKSDLEESKEWIKKSNQKLDSIGNWH-NH2
627	Ac-NQQEKNEQELLELDKWASLWNWFNITNWLWYIKIFI-NH2
627	Ac-NQQEKNEQELLELDKWASLWNWFNITNWLWYIKIPI-NH2
628	Ac-QNQQEKNEQELLELDKWASLWNWFNITNWLWYIKIF-NH2
629	Ac-SQNQQEKNEQELLELDKWASLWNWFNITNWLWYIKI-NH2
630	Ac-ESQNQQEKNEQELLELDKWASLWNWFNITNWLWYIK-NH2
631	Ac-EESQNQQEKNEQELLELDKWASLWNWFNITNWLWYI-NH2
632	Ac-IEESQNQQEKNEQELLELDKWASLWNWFNITNWLWY-NH2
633	Ac-LIEESQNQQEKNEQELLELDKWASLWNWFNITNWLW-NH2
634	Ac-SLIEESQNQQEKNEQELLELDKWASLWNWFNITNWL-NH2
635	Ac-HSLIEESQNQQEKNEQELLELDKWASLWNWFNITNW-NH2
636	Ac-IHSLIEESQNQQEKNEQELLELDKWASLWNWFNITN-NH2
637	Ac-LIHSLIEESQNQQEKNEQELLELDKWASLWNWFNIT-NH2

T No.	Sequence
638	Ac-SLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNI-NH2
639	Ac-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFN-NH2
640	Ac-NYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNW-NH2
641	Ac-NNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWN-NH2
642	Ac-INNYTSLIHSLIEESQNQQEKNEQELLELDKWASLW-NH2
643	Ac-EINNYTSLIHSLIEESQNQQEKNEQELLELDKWASL-NH2
644	Ac-REINNYTSLIHSLIEESQNQQEKNEQELLELDKWAS-NH2
645	Ac-DREINNYTSLIHSLIEESQNQQEKNEQELLELDKWA-NH2
646	Ac-WDREINNYTSLIHSLIEESQNQQEKNEQELLELDKW-NH2
647	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQELLELDK-NH2
648	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQELLELD-NH
649	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2
650	Ac-TWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLE-NH2
651	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELL-NH2
652	Ac-NMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
653	Ac-NNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQE-NH2
654	Ac-WNNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQ-NH2
655	Ac-IWNNMTWMEWDREINNYTSLIHSLIEESQNQQEKNE-NH2
656	Ac-QIWNNMTWMEWDREINNYTSLIHSLIEESQNQQEKN-NH2
657	Ac-EQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQEK-NH2
658	Ac-LEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQE-NH2
659	Ac-SLEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQ-NH2
660	Ac-KSLEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQ-NH2
661	Ac-NKSLEQIWNNMTWMEWDREINNYTSLIHSLIEESQN-NH2
662	Ac-SLAFIRKSDELLHNVNAGKST-NH2
663	Ac-FDASISQVNEKINQSLAFIRK-NH2
664	Ac-YTSLIHSLIEESQQQQEKQEQELLELDKWASLWNWF-NH2
665	Ac-FDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2
666	Ac-FDASISQVNEKINQSLAFIRKSDELLHNVNA-NH2
667	Ac-FDASISQVNEKINQSLAFIRKSDELLHNV-NH2
668	Ac-FDASISQVNEKINQSLAFIRKSDELLH-NH2
669	Ac-FDASISQVNEKINQSLAFIRKSDEL-NH2
670	Ac-FDASISQVNEKINQSLAFIRKSD-NH2
671	Ac-ASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
672	Ac-ISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
673	Ac-QVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
674	Ac-NEKINQSLAFIRKSDELLHNVNAGKST-NH2
675	Ac-KINQSLAFIRKSDELLHNVNAGKST-NH2
676	Ac-NQSLAFIRKSDELLHNVNAGKST-NH2
677	Ac-FWNWLSAWKDLELYPGSLELDKWASLWNWF-NH2
678	Ac-CGGNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
679	Ac-CGGYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
680	YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF
681	NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ
682	Ac-EKNMYELQKLNSWDVFTNWLDFTSWVRYIQYIQYGV-NH2
683	Ac-QEKNMYELQKLNSWDVFTNWLDFTSWVRYIQYIQYG-NH2
684	Ac-QQEKNMYELQKLNSWDVFTNWLDFTSWVRYIQYIQY-NH2
685	Ac-IQQEKNMYELQKLNSWDVFTNWLDFTSWVRYIQYIQ-NH2
686	Ac-QIQQEKNMYELQKLNSWDVFTNWLDFTSWVRYIQYI-NH2
687	Ac-AQIQQEKNMYELQKLNSWDVFTNWLDFTSWVRYIQY-NH2

T No.	Sequence
688	Ac-QAQIQQEKNMYELQKLNSWDVFTNWLDFTSWVRYIQ-NH2
689	Ac-EQAQIQQEKNMYELQKLNSWDVFTNWLDFTSWVRYI-NH2
690	Ac-LEQAQIQQEKNMYELQKLNSWDVFTNWLDFTSWVRY-NH2
691	Ac-SLEQAQIQQEKNMYELQKLNSWDVFTNWLDFTSWVR-NH2
692	Ac-QSLEQAQIQQEKNMYELQKLNSWDVFTNWLDFTSWV-NH2
693	Ac-SQSLEQAQIQQEKNMYELQKLNSWDVFTNWLDFTSW-NH2
694	Ac-ISQSLEQAQIQQEKNMYELQKLNSWDVFTNWLDFTS-NH2
695	Ac-NISQSLEQAQIQQEKNMYELQKLNSWDVFTNWLDFT-NH2
696	Ac-ANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWLDF-NH2
697	Ac-EANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWLD-NH2
699	Ac-YLEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNW-NH2
700	Ac-YTSLIHSLIEESQNQQEKNEQEL-NH2
701	Ac-YTSLIHSLIEESQNLQEKNEQELLELDKWASLWNWF-NH2
702	Ac-YTSLIHSLIEESQNQQEKLEQELLELDKWASLWNWF-NH2
703	Ac-YTSLIHSLIEESQNQQEKNEQELLEFDKWASLWNWF-NH2
704	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKPASLWNWF-NH2
705	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASPWNWF-NH2
706	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNSF-NH2
707	Biotin NH(CH2)4CO-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
708	Biotin NH(CH2)6CO-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
709	FMOC-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF
710	FMOC-NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ
711	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQE-NH2
712	Ac-LIEESQNQQEKNEQELLELDKWASLWNWF-NH2
713	Ac-FWNWLSAWKDLELGGPGSGPGGLELDKWASLWNWF-NH2
714	Ac-LIHSLIEESQNQQEKNEQELLELDKWASL-NH2
715	Ac-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
716	Ac-LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
718	FMOC-GGGGGYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
719	Ac-HSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
720	Ac-YTSLIYSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
721	Ac-YTSLIHSLIEKSQNQQEKNEQELLELDKWASLWNWF-NH2
722	Ac-YTSLIHSSIEESQNQQEKNEQELLELDKWASLWNWF-NH2
723	Ac-LEANISQLLEQAQIQQEKNMYELQKLNSWDVFTNWL-NH2
724	Ac-SLEECDSELEIKRYKNRVASRKCRAKFKQLLQHYR-NH2
725	Ac-LEECDSELEIKRYKNRVASRKCRAKFKQLLQHYRE-NH2
726	Ac-EECDSELEIKRYKNRVASRKCRAKFKQLLQHYREV-NH2
727	Ac-ECDSELEIKRYKNRVASRKCRAKFKQLLQHYREVA-NH2
728	Ac-CDSELEIKRYKNRVASRKCRAKFKQLLQHYREVAA-NH2
729	Ac-DSELEIKRYKNRVASRKCRAKFKQLLQHYREVAAA-NH2
730	Desaminotyrosine-FDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
731	WASLWNW-NH2
732	Ac-EAQQHLLQLTVWGIKQLQARILAVERYLKDQQLLGIWG-NH2
733	Ac-IEAQQHLLQLTVWGIKQLQARILAVERYLKDQQLLGIW-NH2
734	Ac-AIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQLLGI-NH2
735	Ac-RAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQLLG-NH2
736	Ac-LRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQLL-NH2
737	Ac-LLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQL-NH2
738	Ac-NLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQ-NH2
739	Ac-QNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKD-NH2

T No.	Sequence
740	Ac-QQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLK-NH2
741	Ac-QQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYL-NH2
742	Ac-VQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERY-NH2
743	Ac-IVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVER-NH2
744	Ac-GIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVE-NH2
745	Ac-SGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAV-NH2
758	Ac-RSMTLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQLTV-NH2
760	Ac-GARSMTLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQL-NH2
764	Ac-GSTMGARSMTLTVQARQLLSGIVQQQNNLLRAIEAQQH-NH2
765	Ac-GSTMGARSMTLTVQARQLLSGIVQQQNNLLRAIEAQQH-NH2
766	Ac-EGSTMGARSMTLTVQARQLLSGIVQQQNNLLRAIEAQQ-NH2
767	Ac-RAKFKQLLQHYREVAAAKSSENDRLRLL-NH2
768	Ac-AKFKQLLQHYREVAAAKSSENDRLRLLL-NH2
769	Ac-KFKQLLQHYREVAAAKSSENDRLRLLLK-NH2
770	Ac-FKQLLQHYREVAAAKSSENDRLRLLLKQ-NH2
771	Ac-RAKFKQELQHYREVAAAKSSENDRLRLLLKQMCPS-NH2
772	DKWASLWNWF-NH2
773	Biotin-FDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
774	Ac-YDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
775	Ac-YDASISQVNEKINQSLAYIRKSDELLHNVNAGKST-NH2
776	Ac-FDASISQVNEKINQSLAYIRKSDELLHNVNAGKST-NH2
777	Ac-FDASISQVQEKIQQSLAFIRKSDELLHQVQAGKST-NH2
778	Ac-FDASISQVNEKINQALAFIRKADELLHNVNAGKST-NH2
779	Ac-FDASISQVNEKINQALAFIRKSDELLHNVNAGKST-NH2
780	Ac-FDASISQVNEKINQSLAFIRKADELLHNVNAGKST-NH2
781	Ac-YDASISQVQEEIQQALAFIRKADELLEQVQAGKST-NH2
782	Ac-FDASISQVNEKINQSLAFIRKSDELLENVNAGKST-NH2
783	Ac-FDASISQVNEEINQSLAFIRKSDELLHNVNAGKST-NH2
784	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLENV-NH2
785	Ac-VFPSDEFDASISQVNEEINQSLAFIRKSDELLENV-NH2
786	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
787	Ac-VFPSDEFDASISQVNEEINQSLAFIRKSDELLHNV-NH2
788	Ac-SNKSLEQIWNNMTWMEWDREINNYTSLIHSLIEESQ-NH2
789	Ac-WSNKSLEQIWNNMTWMEWDREINNYTSLIHSLIEES-NH2
790	Ac-SWSNKSLEQIWNNMTWMEWDREINNYTSLIHSLIEE-NH2
791	Ac-ASWSNKSLEQIWNNMTWMEWDREINNYTSLIHSLIE-NH2
792	Ac-NASWSNKSLEQIWNNMTWMEWDREINNYTSLIHSLI-NH2
793	Ac-WNASWSNKSLEQIWNNMTWMEWDREINNYTSLIHSL-NH2
793	Ac-WNASWSNKSLEQIWNNMTWMEWDREINNYTSLIHSL-NH2
794	Ac-PWNASWSNKSLEQIWNNMTWMEWDREINNYTSLIHS-NH2
795	Ac-VPWNASWSNKSLEQIWNNMTWMEWDREINNYTSLIH-NH2
796	Ac-AVPWNASWSNKSLEQIWNNMTWMEWDREINNYTSLI-NH2
797	Ac-TAVPWNASWSNKSLEQIWNNMTWMEWDREINNYTSL-NH2
798	Ac-TTAVPWNASWSNKSLEQIWNNMTWMEWDREINNYTS-NH2
800	Ac-AAASDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
801	Ac-VFPAAAFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
802	Ac-VFPSDEAAASISQVNEKINQSLAFIRKSDELLHNV-NH2
803	Ac-VFPSDEFDAAAAQVNEKINQSLAFIRKSDELLHNV-NH2
804	Ac-VFPSDEFDASISAAAEKINQSLAFIRKSDELLHNV-NH2
805	Ac-VFPSDEFDASISQVNAAANQSLAFIRKSDELLHNV-NH2

T No.	Sequence
806	Ac-VFPSDEFDASISQVNEKIAAALAFIRKSDELLHNV-NH2
807	Ac-VFPSDEFDASISQVNEKINQSAAAIRKSDELLHNV-NH2
808	Ac-VFPSDEFDASISQVNEKINQSLAFAAASDELLHNV-NH2
809	Ac-VFPSDEFDASISQVNEKINQSLAFIRKAAALLHNV-NH2
810	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDEAAANV-NH2
811	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLAAA-NH2
812	Ac-VYPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
813	Ac-AAAAIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
814	Ac-YTSLIHSLIEESQQQQEKNEQELLELDKWASLWNWF-NH2
815	Ac-YTSLIHSLIEESQNQQEKQEQELLELDKWASLWNWF-NH2
816	Ac-QIWNNMTWMEWDREINNYTSLIHSLIEESQNQQEKQ-NH2
817	Ac-QIWNNMTWMEWDREINNYTSLIHSLIEESQQQQEKN-NH2
818	Ac-QIWNNMTWMEWDREINNYTSLIHSLIEESQQQQEKQ-NH2
819	Ac-NKSLEQIWNNMTWMEWDREINNYTSLIHSLIEESQQ-NH2
820	Ac-FDASISQVNEKINQSLAFIEESDELLHNVNAGKST-NH2
821	Ac-ACIRKSDELCL-NH2
823	Ac-YTSLIHSLIEESQNQQEKDEQELLELDKWASLWNWF-NH2
824	Ac-YTSLIHSLIEESQDQQEKNEQELLELDKWASLWNWF-NH2
825	Ac-YTSLIHSLIEESQDQQEKDEQELLELDKWASLWNWF-NH2
826	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWDWF-NH2
841	Ac-LEANITQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-NH2
842	Ac-LEANISASLEQAQIQQEKNMYELQKLNSWDVFTNWL-NH2
843	Ac-LEANISALLEQAQIQQEKNMYELQKLNSWDVFTNWL-NH2
844	Ac-LEANITALLEQAQIQQEKNMYELQKLNSWDVFTNWL-NH2
845	Ac-LEANITASLEQAQIQQEKNMYELQKLNSWDVFTNWL-NH2
845	Ac-LEANITASLEQAQIQQEKNMYELQKLNSWDVFTNWL-NH2
846	Ac-RAKFKQLLQHYREVAAAKSSENDRLRLLLKQMUPS-NH2
847	Ac-Abu-DDE-Abu-MNSVKNGTYDYPKYEEESKLNRNEIKGVKL-NH2
856	Ac-WQEWEQKVRYLEANISQSLEQAQIQQEKNMYELQKL-NH2
860	Ac-DEYDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2
861	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWN-NH2
862	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLW-NH2
863	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASL-NH2
864	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWAS-NH2
865	Ac-QARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
866	Ac-DREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
867	Ac-NNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDK-NH2
868	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWAAA-NH2
869	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWAAAANWF-NH2
870	Ac-YTSLIHSLIEESQNQQEKNEQELLELDAAASLWNWF-NH2
871	Ac-YTSLIHSLIEESQNQQEKNEQELLAAAKWASLWNWF-NH2
872	Ac-YTSLIHSLIEESQNQQEKNEQAAAELDKWASLWNWF-NH2
873	Ac-YTSLIHSLIEESQNQQEKAAAELLELDKWASLWNWF-NH2
874	Ac-YTSLIHSLIEESQNQAAANEQELLELDKWASLWNWF-NH2
875	Ac-YTSLIHSLIEESAAAQEKNEQELLELDKWASLWNWF-NH2
876	Ac-YTSLIHSLIAAAQNQQEKNEQELLELDKWASLWNWF-NH2
877	Ac-YTSLIHAAAEESQNQQEKNEQELLELDKWASLWNWF-NH2
878	Ac-YTSAAASLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
879	Ac-EIWNNMTWMEWDRENEKINQSLAFIRKSDELLHNV-NH2
880	Ac-YISEVNEEINQSLAFIRKADELLENVDKWASLWNWF-NH2

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881	Ac-TSVITIELSNIKENKANGTDAKVKLIKQELDKYKN-NH2
882	YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFMG-NH2
883	Ac-NEKINQSLAFIRKSDELLHNV-NH2
884	Biotin-YDPLVFPSDEFDASISQVNEKINQSLAFIRKSDEL-NH2
885	Biotin-PLVFPSDEFDASISQVNEKINQSLAFIRKSDELLH-NH2
886	Biotin-VFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
887	Biotin-DEFDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2
888	Biotin-VYPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
889	Biotin-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
890	Ac-VYPSDEFDASISQVQEEIQQALAFIRKADELLEQV-NH2
891	Ac-NYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
892	Ac-NNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
893	Ac-INNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
894	Ac-EINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
895	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFN-NH2
896	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNI-NH2
897	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNIT-NH2
898	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNITN-NH2
899	Ac-YDPLVFPSDEFDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2
900	Ac-NYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFN-NH2
901	Ac-NNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNI-NH2
905	Ac-KCRAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTPD-NH2
906	Ac-RAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTPD-NH2
907	Ac-VYPSDEYDASISQVNEEINQALAYIAAADELLENV-NH2
909	Ac-YDASISQVNEEINQALAYIRKADELL-NH2
910	Ac-M-Nle-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2
911	Ac-KNGTYDYPKYEEESKLNRNEIKGVKLSSMGVYQI-NH2
912	Ac-VTEKIQMASDNINDLIQSGVNTRLLTIQSHVQNYI-NH2
913	QNQQEKNEQELLELDKWASLWNWF-NH2
914	Ac-QNQQEKNEQELLELDKWASLWNWF-NH2
915	LWNWF-NH2
916	ELLELDKWASLWNWF-NH2
917	EKNEQELLELDKWASLWNWF-NH2
918	SLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
919	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNW
920	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWN
921	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLW
922	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASL
923	TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
924	SLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
925	LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
926	IHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
940	Ac-AAVALLPAVLLALLAPSELEIKRYKNRVASRKCRAKFKQLLQHYREVAAAK-NH2
941	Ac-AAVALLPAVLLALLAPCRAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCP-NH2
942	Ac-YTSLIHSLIEESQNQQEKNNNIERDWEMWTMNNWIQ-NH2
944	VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
945	Ac-LMQLARQLMQLARQMKQLADSLMQLARQVSRLESA-NH2
946	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELL-NH2
947	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2
948	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2

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949	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQELLE-NH2
950	Biotin-W-Nle-EWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2
951	Ac-YLEYDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2
952	Ac-IKQFINMWQEVGKAMYA-NH2
953	Ac-IRKSDELL-NH2
954	Decanoyl-IRKSDELL-NH2
955	Acetyl-Aca-Aca-IRKSDELL-NH2
956	Ac-YDASISQV-NH2
957	Ac-NEKINQSL-NH2
958	Ac-SISQVNEEINQALAYIRKADELL-NH2
959	Ac-QVNEEINQALAYIRKADELL-NH2
960	Ac-EEINQALAYIRKADELL-NH
961	Ac-NQALAYIRKADELL-NH2
962	Ac-LAYIRKADELL-NH2
963	FDASISQVNEKINQALAFIRKSDELL-NH2
964	Ac-W-Nle-EWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2
965	Ac-ASRKCRAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDS-NH2
967	Ac-WLEWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2
968	Ac-YVKGEPIINFYDPLVFPSDEFDASISQVNEKINQSL-NH2
969	Ac-VYPSDEYDASISQVNEEINQSLAYIRKADELLHNV-NH2
970	Ac-YDASISQVNEEINQALAYIRKADELLENV-NH2
971	Ac-YDASISQVNEEINQALAYIRKADELLE-NH2
972	Ac-VYPSDEYDASISQVNEEINQALAYIRKAAELLHNV-NH2
973	Ac-VYPSDEYDASISQVNEEINQALAYIRKALELLHNV-NH2
974	Decanoyl-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
975	Ac-VYPSDEYDASISQVNEEINQLLAYIRKLDELLENV-NH2
976	Ac-DEYDASISQVNEKINQSLAFIRKSDELL-NH2
977	Ac-SNDQGSGYAADKESTQKAFDGITNKVNSVIEKTNT-NH2
978	Ac-ESTQKAFDGITNKVNSVIEKTNTQFEAVGKEFGNLEKR-NH2
979	Ac-DGITNKVNSVIEKTNTQFEAVGKEFGNLEKRLENLNK-NH2
980	Ac-DSNVKNLYDKVRSQLRDNVKELGNGAFEFYHK-NH2
981	Ac-RDNVKELGNGAFEFYHKADDEALNSVKNGTYDYPKY-NH2
982	Ac-EFYHKADDEALNSVKNGTYDYPKY-NH2
983	Ac-AAVALLPAVLLALLAPAADKESTQKAFDGITNKVNS-NH2
984	Ac-AAVALLPAVLLALLAPAADSNVKNLYDKVRSQLRDN-NH2
985	Ac-KESTQKAFDGITNKVNSV-NH2
986	Ac-IEKTNTQFEAVGKEFGNLER-NH2
987	Ac-RLENLNKRVEDGFLDVWTYNAELLVALENE-NH2
988	Ac-SNVKNLYDKVRSQLRDN-NH2
989	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
990	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQE-NH2
991	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
992	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQE-NH2
993	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQELLE-NH2
994	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQELL-NH2
995	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
996	Ac-YTKFIYTLLEESQNQQEKNEQELLELDKWASLWNWF-NH2
997	Ac-YMKQLADSLMQLARQVSRLESA-NH2
998	Ac-YLMQLARQMKQLADSLMQLARQVSRLESA-NH2
999	Ac-YQEWERKVDFLEENITALLEEAQIQQEKNMYELQKL-NH2

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1000	Ac-WMAWAAAINNYTSLIHSLIEESQNQQEKNEQEEEEE-NH2
1001	Ac-YASLIAALIEESQNQQEKNEQELLELAKWAALWAWF-NH2
1002	[Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEGGC-NH2]dimer
1003	Ac-YDISIELNKAKSDLEESKEWIKKSNQKLDSIGNWH-NH2
1004	Biotinyl-IDISIELNKAKSDLEESKEWIKKSNQKLDSIGNWH-NH2
1005	Ac-YTSLI-OH
1006	Fmoc-HSLIEE-OH
1007	Fmoc-SQNQQEK-OH
1008	Fmoc-NEQELLEL-OH
1009	Fmoc-DKWASL-OH
1010	Fmoc-WNWF-OH
1011	Ac-AKTLERTWDTLNHLLFISSALYKLNLKSVAQITLSI-NH2
1012	Ac-NITLQAKIKQFINMWQEVGKAMYA-NH2
1013	Ac-LENERTLDFHDSNVKNLYDKVRLQLRDN-NH2
1014	Ac-LENERTLDFHDSNVKNLYDKVRLQLRDNVKELGNG-NH2
1015	Ac-TLDFHDSNVKNLYDKVRLQLRDNVKELGNGAFEF-NH2
1016	Ac-IDISIELNKAKSDLEESKEWIKKSNQKLDSIGNWH-NH2
1021	Biotinyl-SISQVNEEINQALAYIRKADELL-NH2
1022	Biotinyl-SISQVNEEINQSLAYIRKSDELL-NH2
1023	Ac-SISQVNEEINQSLAYIRKSDELL-NH2
1024	Ac-IDISIELNKAKSDLEESKEWIEKSNQELDSIGNWE-NH2
1025	Ac-IDISIELNKAKSDLEESKEWIKKSNQELDSIGNWH-NH2
1026	Ac-IDISIELNKAKSDLEEAKEWIDDANQKLDSIGNWH-NH2
1027	Ac-IDISIELNKAKSDLEESKEWIKKANQKLDSIGNWH-NH2
1028	Ac-IDISIELNKAKSDLEEAKEWIKKSNQKLDSIGNWH-NH2
1029	Biotinyl-NSVALDPIDISIELNKAKSDLEESKEWIKKSNQKL-NH2
1030	Biotinyl-ALDPIDISIELNKAKSDLEESKEWIKKSNQKLDSI-NH2
1031	desAminoTyrosine-NSVALDPIDISIELNKAKSDLEESKEWIKKSNQKL-NH2
1032	desAminoTyrosine-ALDPIDISIELNKAKSDLEESKEWIKKSNQKLDSI-NH2
1033	Ac-YDASISQVNEEINQALAFIRKADEL-NH2
1034	Ac-YDASISQVNEEINQSLAYIRKADELL-NH2
1035	Biotinyl-YDASISQVNEEINQALAYIRKADELL-NH2
1036	Biotinyl-YDASISQVNEEINQSLAFIRKSDELL-NH2
1037	Ac-YDASISQVNEEINQSLAFIRKSDELL-NH2
1038	Ac-WLEWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
1039	Biotinyl-IDISIELNKAKSDLEESKEWIRRSNQKLDSIGNWH-NH2
1044	Ac-YESTQKAFDGITNKVNSVIEKTNTQFEAVGKEFGNLEKR-NH2
1045	Biotin-DEYDASISQVNEKINQSLAFIRKSDELL-NH2
1046	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQELL-NH2
1047	Ac-WQEWEQKVRYLEANISQSLEQAQIQQEKNMYEL-NH2
1048	Ac-WQEWEQKVRYLEANISQSLEQAQIQQEKNEYEL-NH2
1049	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKNEYEL-NH2
1050	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKNMYEL-NH2
1051	Ac-WQEWEQKVRYLEANISQSLEQAQIQQEKNEYELQKL-NH2
1052	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1053	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKNMYELQKL-NH2
1054	Ac-IDISIELNKAKSDLEESKEWIEKSNQKLDSIGNWH-NH2
1055	Ac-EFGNLEKRLENLNKRVEDGFLDVWTYNAELLVALENE-NH2
1056	Ac-EDGFLDVWTYNAELLVLMENERTLDFHDSNVKNLYDKVRMQL-NH2
1057	Ac-SISQVNEKINQSLAFIRKSDELL-NH2

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1058	desaminoTyr-SISQVNEKINQSLAFIRKSDELL-NH2
1059	Ac-SISQVNEKINQSLAYIRKSDELL-NH2
1060	Ac-QQLLDVVKRQQEMLRLTVWGTKNLQARVTAIEKYLKDQ-NH2
1061	YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFC
1062	Ac-FDASISQVNEKINQSLAYIRKSDELL-NH2
1063	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWA
1064	Indole-3-acetyl-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
1065	Indole-3-acetyl-DEFDESISQVNEKINQSLAFIRKSDELL-NH2
1066	Indole-3-acetyl-DEFDESISQVNEKIEQSLAFIRKSDELL-NH2
1067	Indole-3-acetyl-DEFDESISQVNEKIEESLAFIRKSDELL-NH2
1068	Indole-3-acetyl-DEFDESISQVNEKIEESLQFIRKSDELL-NH2
1069	Indole-3-acetyl-GGGGGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
1070	2-Napthoyl-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
1071	desNH2Tyr-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
1072	biotin-ALDPIDISIELNKAKSDLEESKEWIRRSNQKLDSI-NH2
1073	Ac-YDASISQVNEKINQALAYIRKADELLHNVNAGKST-NH2
1074	Ac-VYPSDEYDASISQVNEKINQALAYIRKADELLHNV-NH2
1075	Ac-VYPSDEYDASISQVNEKINQSLAYIRKSDELLHNV-NH2
1076	Ac-WGWGYGYG-NH2
1077	Ac-YGWGWGWGF-NH2
1078	Ac-WQEWEQKVRYLEANITALQEQAQIQAEKAEYELQKL-NH2
1079	Ac-WQEWEQKVRYLEAEITALQEEAQIQAEKAEYELQKL-NH2
1081	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWAS
1082	Ac-VWPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
1083	Ac-SKNISEQIDQIKKDEQKEGTGWGLGGKWWTSDWGV-NH2
1084	Ac-LSKNISEQIDQIKKDEQKEGTGWGLGGKWWTSDWG-NH2
1085	Ac-DLSKNISEQIDQIKKDEQKEGTGWGLGGKWWTSDW-NH2
1086	Ac-EDLSKNISEQIDQIKKDEQKEGTGWGLGGKWWTSD-NH2
1087	Ac-IEDLSKNISEQIDQIKKDEQKEGTGWGLGGKWWTS-NH2
1088	Ac-GIEDLSKNISEQIDQIKKDEQKEGTGWGLGGKWWT-NH2
1089	Ac-IGIEDLSKNISEQIDQIKKDEQKEGTGWGLGGKWW-NH2
1090	2-Napthoyl--PSDEFDASISQVNEKINQSLAFIRKSDELLHNVN-NH2
1091	Ac-VYPSDEYDASISQVNEKINQALAYIRKADELLENV-NH2
1092	Ac-VYPSDEFDASISQVNEKINQALAFIRKADELLENV-NH2
1093	Ac-VYPSDEYDASISQVNEKINQALAYIREADELLENV-NH2
1094	Biotinyl-YDASISQVNEKINQSLAFIRESDELL-NH2
1095	Ac-AIGIEDLSKNISEQIDQIKKDEQKEGTGWGLGGKW-NH2
1096	Ac-AAIGIEDLSKNISEQIDQIKKDEQKEGTGWGLGGK-NH2
1097	Ac-DAAIGIEDLSKNISEQIDQIKKDEQKEGTGWGLGG-NH2
1098	Ac-PDAAIGIEDLSKNISEQIDQIKKDEQKEGTGWGLG-NH2
1099	Ac-NITDKIDQIIHDFVDKTLPDQGDNDNWWTGWRQWI-NH2
1100	Ac-KNITDKIDQIIHDFVDKTLPDQGDNDNWWTGWRQW-NH2
1101	Ac-TKNITDKIDQIIHDFVDKTLPDQGDNDNWWTGWRQ-NH2
1102	Ac-WTKNITDKIDQIIHDFVDKTLPDQGDNDNWWTGWR-NH2
1103	Ac-DWTKNITDKIDQIIHDFVDKTLPDQGDNDNWWTGW-NH2
1104	Ac-HDWTKNITDKIDQIIHDFVDKTLPDQGDNDNWWTG-NH2
1105	Ac-PHDWTKNITDKIDQIIHDFVDKTLPDQGDNDNWWT-NH2
1106	Ac-EPHDWTKNITDKIDQIIHDFVDKTLPDQGDNDNWW-NH2
1107	Ac-IEPHDWTKNITDKIDQIIHDFVDKTLPDQGDNDNW-NH2
1108	Ac-AIEPHDWTKNITDKIDQIIHDFVDKTLPDQGDNDN-NH2

T No.	Sequence
1109	Ac-AAIEPHDWTKNITDKIDQIIHDFVDKTLPDQGDND-NH2
1110	Ac-DAAIEPHDWTKNITDKIDQIIHDFVDKTLPDQGDN-NH2
1111	Ac-LSPTVWLSVIWMMWYWGPSLYSILSPFLPLLPIFF-NH2
1112	Ac-GLSPTVWLSVIWMMWYWGPSLYSILSPFLPLLPIF-NH2
1113	Ac-VGLSPTVWLSVIWMMWYWGPSLYSILSPFLPLLPI-NH2
1114	Ac-FVGLSPTWLSVIWMMWYWGPSLYSILSPFLPLLP-NH2
1115	Ac-WFVGLSPTVWLSVIWMMWYWGPSLYSILSPFLPLL-NH2
1116	Ac-QWFVFLSPTVWLSVIWMMWYWGPSLYSILSPFLPL-NH2
1117	Ac-VQWFVGLSPTVWLSVIWMMWYWGPSLYSILSPFLP-NH2
1118	Ac-FVQWFVGLSPTVWLSVIWMMWYWGPSLYSILSPFL-NH2
1119	Ac-PFVQWFVGLSPTVWLSVIWMMWYWGPSLYSILSPF-NH2
1120	Ac-VPFVQWFVGLSPTVWLSVIWMMWYWGPSLYSILSP-NH2
1121	Ac-LVPFVQWFVGLSPTVWLSVIWMMWYWGPSLYSILS-NH2
1122	H-NHTTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKW-OH
1123	H-QARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-OH
1124	Ac-VYPSDEFDASISQVNEKINQSLAFIREADELLENV-NH2
1125	Ac-VFPSDEFDASISQVNEKINQSLAYIREADELLENV-NH2
1126	Ac-DEFDASISQVNEKINQSLAYIREADELL-NH2
1127	Ac-NEQELLELDKWASLWNWFGGGGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
1128	Ac-LELDKWASLWNWFGGGGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
1129	Naphthoyl-EGEGEGEGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
1130	Ac-ASRKCRAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDV-NH2
1131	Naphthoyl-GDEEDASISQVNEKINQSLAFIRKSDELL-NH2
1132	Naphthoyl-GDEEDASESQVNEKINQSLAFIRKSDELL-NH2
1133	Naphthoyl-GDEEDASESQQNEKINQSLAFIRKSDELL-NH2
1134	Naphthoyl-GDEEDASESQQNEKQNQSLAFIRKSDELL-NH2
1135	Naphthoyl-GDEEDASESQQNEKQNQSEAFIRKSDELL-NH2
1136	Ac-WGDEFDESISQVNEKIEESLAFIRKSDELL-NH2
1137	Ac-YTSLGGDEFDESISQVNEKIEESLAFIRKSDELLGGWNWF-NH2
1138	Ac-YTSLIHSLGGDEFDESISQVNEKIEESLAFIRKSDELLGGWASLWNWF-NH
1139	2-Naphthoyl-GDEFDESISQVNEKIEESLAFIRKSDELL-NH2
1140	2-Naphthoyl-GDEEDESISQVNEKIEESLAFIRKSDELL-NH2
1141	2-Naphthoyl-GDEEDESISQVQEKIEESLAFIRKSDELL-NH2
1142	2-Naphthoyl-GDEEDESISQVQEKIEESLLFIRKSDELL-NH2
1143	Biotin-GDEYDESISQVNEKIEESLAFIRKSDELL-NH2
1144	2-Naphthoyl-GDEYDESISQVNEKIEESLAFIRKSDELL-NH2
1145	Ac-YTSLIHSLIDEQEKIEELAFIRKSDELLELDKWNWF-NH2
1146	VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1147	Ac-NNLLRAIEAQQHLLQLTVWGSKQLQARILAVERYLKDQ-NH2
1148	GGGVYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1149	Ac-NNLLRAIEAQQHLLQLTVWGEKQLQARILAVERYLKDQ-NH2
1150	Ac-PTRVNYILIIGVLVLAbuEVTGVRADVHLL-NH2
1151	Ac-PTRVNYILIIGVLVLAbuEVTGVRADVHLLEQPGNLW-NH2
1152	Ac-PEKTPLLPTRVNYILIIGVLVLAbuEVTGVRADVHLL-NH2
1153	AhaGGGVYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1155	Ac-YTSLIHSLGGDEFDESISQVNEKIEESLAFIRKSDELL-NH2
1156	Ac-YTSLGGDEFDESISQVNEKIEESLAFIRKSDELL-NH2
1157	Ac-DEFDESISQVNEKIEESLAFIRKSDELLGGWASLWNWF-NH2
1158	Ac-DEFDESISQVNEKIEESLAFIRKSDELLGGWNWF-NH2
1159	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKASLWNWF-NH2

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1160	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKSLWNWF-NH2
1161	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKLWNWF-NH2
1162	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWNWF-NH2
1163	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKASLWNWF-NH2
1164	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKSLWNWF-NH2
1165	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKLWNWF-NH2
1166	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWNWF-NH2
1167	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWN-NH2
1168	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASL-NH2
1169	(Pyr)HWSY(2-napthyl-D-Ala)LRPG-NH2
1170	Ac-WNWFDEFDESISQVNEKIEESLAFIRKSDELLWNWF-NH2
1171	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKYASLYNYF-NH2
1172	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKYAYLYNYF-NH2
1173	2-Naphthoyl-AcaAcaAcaDEFDESISQVNEKIEESLAFIRKSDELLAcaAcaAcaW-NH2
1174	2-Naphthoyl-AcaAcaAcaGDEFDESISQVNEKIEESLAFIRKSDELLGAcaAcaAcaW-NH2
1175	2-Naphthoyl-GDEFDESISQVNEKIEESLAFIRESDELL-NH2
1176	2-Naphthoyl-GDEFDESISQVNEKIEESLAFIEESDELL-NH2
1177	Ac-WQEWEQKVNYLEANITALLEQAQIQQEKNEYELQKL-NH2
1178	Ac-WQEWEQKVDYLEANITALLEQAQIQQEKNEYELQKL-NH2
1179	Ac-WQEWEQKVRWLEANITALLEQAQIQQEKNEYELQKL-NH2
1180	Ac-WQEWEKQVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1181	Ac-WQEWEHQVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1182	Ac-WQEWEHKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1183	Ac-WQEWDREVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1184	Ac-WQEWEREVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1185	Ac-WQEWERQVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1186	Ac-WQEWEQKVKYLEANITALLEQAQIQQEKNEYELQKL-NH2
1187	Ac-WQEWEQKVRFLEANITALLEQAQIQQEKNEYELQKL-NH2
1188	Ac-VNalPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1189	Ac-VNalPSDENalDASISQVNEEINQALAYIRKADELLENV-NH2
1190	Ac-VNalPSDEYDASISQVNEEINQALANalIRKADELLENV-NH2
1191	Ac-VYPSDEFDASISQVNEKINQSLAFIREADELLFNFF-NH2
1192	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLFNFF-NH2
1193	Ac-YTSLITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2
1194	Ac-YTSLITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1195	Ac-YTSLITALLEQAQIQQEKNEYELQKLDEWASLWEWF-NH2
1196	Ac-YTSLITALLEQAQIQQEKNEYELQELDEWASLWEWF-NH2
1197	Ac-YTSLITALLEEAQIQQEKNEYELQELDEWASLWEWF-NH2
1198	Naphthoyl-Aua-Aua-Aua-TALLEQAQIQQEKNEYELQKLAua-Aua-Aua-W-NH2
1199	Ac-WAAWEQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1200	Ac-WQEAAQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1201	Ac-WQEWAAKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1202	Ac-WQAAEQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1203	Ac-WQEWEAAVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1204	Ac-WQEWEQAARYLEANITALLEQAQIQQEKNEYELQKL-NH2
1205	Ac-WQEWEQKAAYLEANITALLEQAQIQQEKNEYELQKL-NH2
1206	Ac-WQEWEQKVAALEANITALLEQAQIQQEKNEYELQKL-NH2
1207	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKNEYELQKLGGGGWASLWNF-NH2
1208	2-Naphthoyl-GDEFDASISQVNEKINQSLAFIRKSDELT-NH2
1209	2-Naphthoyl-GDEFDASISQVNEKINQSLAFTRKSDELT-NH2

T No.	Sequence
1210	2-Naphthoyl-GDEFDASISQVNEKTNQSLAFTRKSDELT-NH2
1211	2-Naphthoyl-GDEFDASISQTNEKTNQSLAFTRKSDELT-NH2
1212	2-Naphthoyl-GDEFDASTSQTNEKTNQSLAFTRKSDELT-NH2
1213	2-Naphthoyl-GDEYDASTSQTNEKTNQSLAFTRKSDELT-NH2
1214	2-Naphthoyl-GDEFDEEISQVNEKIEESLAFIRKSDELL-NH2
1215	2-Naphthoyl-GDEFDASISQVNEKINQSLAFIRKSDELA-NH2
1216	2-Naphthoyl-GDEFDASASQANEKANQSLAFARKSDELA-NH2
1217	2-Naphthoyl-GDEFDESISQVNEKIEESLAFTRKSDELL-NH2
1218	2-Naphthoyl-GDEFDESISQVNEKTEESLAFIRKSDELL-NH2
1219	2-Naphthoyl-GDEFDESISQTNEKIEESLAFIRKSDELL-NH2
1220	2-Naphthoyl-GDEFDESTSQVNEKIEESLAFIRKSDELL-NH2
1221	Ac-WNWFDEFDESTSQVNEKIEESLAFIRKSDELLWNWF-NH2
1222	Ac-WNWFDEFDESTSQTNEKIEESLAFIRKSDELLWNWF-NH2
1223	Ac-WNWFDEFDESTSQTNEKTEESLAFIRKSDELLWNWF-NH2
1224	Ac-LQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVAL-NH2
1225	Ac-YTNLIYTLLEESQNQQEKNEQELLELDKWASLWSWF-NH2
1226	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2
1227	Ac-NNMTWQEWEQKVRYLEANITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2
1230	Ac-WNWFIEESDELLWNWF-NH2
1231	2-Naphthoyl-GFIEESDELLW-NH2
1232	Ac-WFIEESDELLW-NH2
1233	2-Naphthoyl-GFNFFIEESDELLFNFF-NH2
1234	2-Naphthoyl-GESDELW-NH2
1235	Ac-WNWFGDEFDESISQVQEEIEESLAFIEESDELLGGWNWF-NH2
1236	Ac-WNWFIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1237	Ac-YTSLITALLEQAQIQQEENEYELQALDEWASLWEWF-NH2
1238	Ac-YTSLIHSLGGDEFDESISQVNEEIEESLAFIEESDELLGGWASLWNWF-NH2
1239	2-Naphthoyl-GDEFDESISQVQEEIEESLAFIEESDELL-NH2
1240	H-QARQLLSSIMQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-OH
1241	Ac-CPKYVKQNTLKLATGMRNVPEKQTR-NH2
1242	Ac-GLFGAIAGFIENGWEGMIDGWYGFRHQNSC-NH2
1243	Ac-LNFLGGT-NH2
1244	Ac-LDSWWTSLNFLGGT-NH2
1245	Ac-ILTIPQSLDSWWTSLNFLGGT-NH2
1246	Ac-GFFLLTRILTIPQSLDSWWTSLNFLGGT-NH2
1247	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2
1248	Ac-WNWFITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2
1249	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1250	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKIEYELQKL-NH2
1251	Ac-WQEWEQKVRYLEAQITALLEQAQIQQEKIEYELQKL-NH2
1252	Ac-KENKANGTDAKVKLIKQELDKYKNAVTELQLLMQS-NH2
1253	Ac-NIKENKANGTDAKVKLIKQELDKYKNAVTELQLLM-NH2
1254	(FS)-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1255	2-Naphthoyl-GWNWFAcaDEFDESISQVQEEIEESLAFIEESDELLAcaWNWF-NH2
1256	Ac-WNWFGDEFDESISQVNEKIEESLAFIEESDELLGWNWF-NH2
1257	Ac-WNWFGDEFDESISQVNEKIEESLAFIRKSDELLGWNWF-NH2
1258	Ac-WNWF-Aca-DEFDESISQVNEKIEESLAFIRKSDELL-Aca-WNWF-NH2
1259	Ac-WNWF-Aca-DEFDESISQVNEKIEESLAFIEESDELL-Aca-WNWF-NH2
1260	Ac-EESQNQQEKNEQELLELDKWA-NH2
1261	EESQNQQEKNEQELLELDKWA

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1262	Ac-CGTTDRSGAPTYSWGANDTDVFVLNNTRPPLGNWFG-NH2
1263	Ac-GVEHRLEAACNWTRGERADLEDRDRSELSP-NH2
1264	Ac-CVREGNASRAWVAVTPTVATRDGKLPT-NH2
1265	Ac-CFSPRHHWTTQDANASIYPG-NH2
1266	Ac-LQHYREVAAAKSSENDRLRLLLKQMCPSLDVDS-NH2
1267	Ac-WQEWDREISNYTSLITALLEQAQIQQEKNEYELQKLDEWASLWEWF-NH2
1268	Ac-CWQEWDREISNYTSLITALLEQAQIQQEKNEYELQKLDEWASLWEWFC-NH2
1269	Ac-WQEWDREISNYTSLITALLEQAQIQQEKNEYELQKLDEWEWF-NH2
1270	Ac-CWQEWDREISNYTSLITALLEQAQIQQEKNEYELQKLDEWEWFC-NH2
1271	Ac-GQNSQSPTSNHSPTSAPPTAPGYRWA-NH2
1272	Ac-PGSSTTSTGPARTALTTAQGTSLYPSA-NH2
1273	Ac-PGSSTTSTGPARTALTTAQGTSLYPSAAATKPSDGNATA-NH2
1275	Ac-WQEWDREITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2
1276	Ac-WQEWDREITALLEQAQIQQEKNEYELQKLDEWASLWEWF-NH2
1277	Ac-WQEWDREITALLEQAQIQQEKNEYELQKLDEWEWF-NH2
1278	Ac-WQEWDREITALLEQAQIQQEKNEYELQKLDEWEWF-NH2
1279	Ac-WQEWEREITALLEQAQIQQEKNEYELQKLIEWEWF-NH2
1280	Ac-WQEWEREITALLEQAQIQQEKIEYELQKLDEWEWF-NH2
1281	Ac-WQEWEITALLEQAQIQQEKNEYELQKLDEWEWF-NH2
1282	Ac-WQEWEITALLEQAQIQQEKNEYELQKLIEWEWF-NH2
1283	Ac-WQEWEITALLEQAQIQQEKIEYELQKLDEWEWF-NH2
1284	Ac-WQEWEITALLEQAQIQQEKIEYELQKLIEWEWF-NH2
1285	Ac-WQEWDREIDEYDASISQVNEKINQALAYIREADELWEWF-NH2
1286	Ac-WQEWEREIDEYDASISQVNEKINQALAYIREADELWEWF-NH2
1287	Ac-WQEWEIDEYDASISQVNEKINQALAYIREADELWEWF-NH2
1288	Ac-WQEWDREIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
1289	Ac-WQEWEREIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
1290	Ac-WQEWEIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
1291	Ac-WQEWDEYDASISQVNEKINQALAYIREADELWEWF-NH2
1292	Ac-WQEWDEYDASISQVNEEINQALAYIREADELWEWF-NH2
1293	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLIEWEWF-NH2
1294	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLIEWASLWEWF-NH2
1295	Ac-WQEWEITALLEQAQIQQEKIEYELQKLIEWASLWEWF-NH2
1298	-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1299	Ac-WVYPSDEYDASISQVNEEINQALAYIRKADELLENVWNWF-NH2
1300	YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1301	Ac-WQEWDEYDASISQVNEKINQALAYIREADELWAWF-NH2
1302	Ac-WQAWDEYDASISQVNEKINQALAYIREADELWAWF-NH2
1303	Ac-WQAWDEYDASISQVNEKINQALAYIREADELWEWF-NH2
1304	Biotin-YDPLVFPSDEFDASISQVNEKINQSLAFIRKSDEL-NH2
1305	Biotin-YDPLVFPSDEFDASISQVNEKINQSLAF-NH2
1306	Biotin-QVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
1307	Ac-WMEWDREI-NH2
1308	Ac-WQEWEQKI-NH2
1309	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLIKWASLWEWF-NH2
1310	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLIEWASLWEWF-NH2
1311	Ac-WQEWEREISAYTSLITALLEQAQIQQEKIEYELQKLIEWEWF-NH2
1312	Ac-WQEWEREISAYTSLITALLEQAQIQQEKIEYELQKEWEWF-NH2
1313	Ac-WQEWEREISAYTSLITALLEQAQIQQEKIEYELQKEWEW-NH2
1314	Ac-WQEWEREISAYTSLITALLEQAQIQQEKIEYELQKLIEWEW-NH2

T No.	Sequence
1315	Ac-FNLSDHSESIQKKFQLMKKHVNKIGVDSDPIGSWLR-NH2
1316	Ac-DHSESIQKKFQLMKKHVNKIGVDSDPIGSWLRGIF-NH2
1317	Ac-WSVKQANLTTSLLGDLLDDVTSIRHAVLQNRA-NH2
1318	Biotin-WMEWDREI-NH2
1319	Biotin-NNMTWMEWDREINNYTSL-NH2
1320	Ac-GAASLTLTVQARQLLSGIVQQQNNLLRAIEAQQHLL-NH2
1321	Ac-ASLTLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQL-NH2
1322	Ac-VSVGNTLYYVNKQEGKSLYVKGEPIINFYDPLVF-NH2
1323	Ac-QHWSYGLRPG-NH2
1324	Ac-WQEWEQKIQHWSYGLRPGWASLWEWF-NH2
1325	Ac-WQEWEQKIQHWSYGLRPGWEWF-NH2
1326	Ac-WNWFQHWSYGLRPGWNWF-NH2
1327	Ac-FNFFQHWSYGLRPGFNFF-NH2
1328	Ac-GAGAQHWSYGLRPGAGAG-NH2
1329	PLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGT
1330	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLAKWASLWEWF-NH2
1331	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLAEWASLWEWF-NH2
1332	Ac-WQEWEQKITALLEQAQIQQEKAEYELQKLAEWASLWEWF-NH2
1333	Ac-WQEWEQKITALLEQAQIQQEKAEYELQKLAEWASLWAWF-NH2
1334	Ac-WQEWEQKITALLEQAQIQQEKAEYELQKLAKWASLWAWF-NH2
1335	Ac-TNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVNK-NH2
1336	Ac-KAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVNKQS-NH2
1337	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIEWEWF-NH2
1338	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIEWEWF-NH2
1339	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLDKWEWF-NH2
1340	Ac-YDPLVFPSDEFDASISQVNEKINQSLAF-NH2
1341	Fluor--VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1342	Fluor-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1344	Ac-SGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARIL-NH2
1345	Ac-QQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
1346	Ac-SGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
1347	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAEWASLWAWF-NH2
1348	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAEWASLWAW-NH2
1349	Ac-WQEWEQKITALLEQAQIQQEKAEYELQKLAEWASLWAW-NH2
1350	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAEWAGLWAWF-NH2
1351	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAEWAGLWAW-NH2
1352	Ac-WQEWEQKITALLEQAQIQQEKAEYELQKLAEWAGLWAW-NH2
1353	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWAGLWEWF-NH2
1354	Ac-WQEWQHWSYGLRPGWEWF-NH2
1355	Ac-WQAWQHWSYGLRPGWAWF-NH2
1356	Biotinyl-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1357	WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF
1358	WQEWEQKITALLEQAQIQQEKIEYELQKLIEWEWF
1361	Ac-AGSTMGARSMTLTVQARQLLSGIVQQQNNLLRAIEAQQ-NH2
1362	Ac-AGSAMGAASLTLSAQSRTLLAGIVQQQQQLLDVVKRQQ-NH2
1363	Ac-AGSAMGAASTALTAQSRTLLAGIVQQQQQLLDVVKRQQ-NH2
1364	Ac-ALTAQSRTLLAGIVQQQQQLLDVVKRQQELLRLTVWGT-NH2
1365	Ac-TLSAQSRTLLAGIVQQQQQLLDVVKRQQEMLRLTVWGT-NH2
1366	Ac-TLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGI-NH2
1367	Ac-WQAWIEYEAELSQVKEKIEQSLAYIREADELWAWF-NH2

T No.	Sequence
1368	Ac-WQAWIEYEASLSQAKEKIEESKAYIREADELWAWF-NH2
1369	Ac-WQAWIEYERLLVQAKLKIAIAKLYIAKELLEWAWF-NH2
1370	Ac-WQAWIEYERLLVQVKLKIAIALLYIAKELLEWAWF-NH2
1371	Ac-WQAWIELERLLVQVKLKLAIAKLEIAKELLEWAWF-NH2
1372	Ac-GEWTYDDATKTFTVTEGGH-NH2
1373	Ac-WQEWEQKIGEWTYDDATKTFTVTEGGHWASLWEWF-NH2
1374	Ac-GEWTYDDATKTFTVTE-NH2
1375	Ac-WQEWEQKIGEWTYDDATKTFTVTEWASLWEWF-NH2
1376	Ac-MHRFDYRT-NH2
1377	Ac-WQEWEQKIMHRFDYRTWASLWEWF-NH2
1378	Ac-MHRFNWSTGGG-NH2
1379	Ac-WQEWEQKIMHRFNWSTGGGWASLWEWF-NH2
1380	Ac-MHRFNWST-NH2
1381	Ac-WQEWEQKIMHRFNWSTWASLWEWF-NH2
1382	Ac-LLVPLARIMTMSSVHGGG-NH2
1383	Ac-WQEWEQKILLVPLARIMTMSSVHGGGWASLWEWF-NH2
1384	Ac-LLVPLARIMTMSSVH-NH2
1385	Ac-WQEWEQKILLVPLARIMTMSSVHWASLWEWF-NH2
1386	TALLEQAQIQQEKNEYELQKLDK
1387	Ac-TALLEQAQIQQEKNEYELQKLDK-NH2
1388	Ac-TALLEQAQIQQEKIEYELQKLIE-NH2
1389	TALLEQAQIQQEKIEYELQKLIE
1390	Ac-QARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERY-NH2
1391	Rhod-QARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERY-NH2
1392	Ac-GAASLTLSAQSRTLLAGIVQQQQQLLDVVKRQQEML-NH2
1393	Ac-GSAMGAASLTLSAQSRTLLAGIVQQQQQLLDVVKRQQEML-NH2
1394	Ac-PALSTGLIHLHQNIVDVQFLFGVGSSIASWAIKWEY-NH2
1395	Ac-PALSTGLIHLHQNIVDVQFLYGVGSSIASWAIK-NH2
1396	Ac-LSTTQWQVLPUSFTTLPALSTGLIHLHQNIVDVQY-NH2
1397	Ac-FRKFPEATFSRUGSGPRITPRUMVDFPFRLWHY-NH2
1398	Ac-DFPFRLWHFPUTINYTIFKVRLFVGGVEHRLEAAUNWTR-NH2♂
1399	Ac-YVGGVEHRLEAAUNWTRGERUDLEDRDRSELSPL-NH2
1400	MVYPSDEYDASISQVNEEINQALAYIRKADELLENV
1402	Ac-GPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGG-NH2
1403	Ac-LGPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLG-NH2
1404	Ac-FLGPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFL-NH2
1405	Ac-YTNTIYTLLEESQNQQEKNEQELLELDKWASLWNWF-NH2
1406	YTNTIYTLLEESQNQQEKNEQELLELDKWASLWNWF
1407	Ac-YTGIIYNLLEESQNQQEKNEQELLELDKWANLWNWF-NH2
1408	YTGIIYNLLEESQNQQEKNEQELLELDKWANLWNWF
1409	Ac-YTSLIYSLLEKSQIQQEKNEQELLELDKWASLWNWF-NH2
1410	YTSLIYSLLEKSQIQQEKNEQELLELDKWASLWNWF
1411	Ac-EKSQIQQEKNEQELLELDKWA-NH2
1412	EKSQIQQEKNEQELLELDKWA
1413	Ac-EQAQIQQEKNEYELQKLDKWA-NH2
1414	Ac-YTSLIGSLIEESQIQQERNEQELLELDRWASLWEWF-NH2
1415	Ac-YTXLIHSLIXESQNQQXKNEQELXELDKWASLWNWF-NH2
1416	Ac-YTXLIHSLIWESQNQQXKNEQELXELD-NH2
1417	Ac-YTSLIHSLIEESQNQQEKNEQELLELD-NH2
1418	Ac-WQEQEXKITALLXQAQIQQXKNEYELXKLDKWASLWEWF-NH2

T No.	Sequence
1419	Ac-XKITALLXQAQIQQXKNEYELXKLDKWASLWEWF-NH2
1420	Ac-WQEWWXKITALLXQAQIQQXKNEYELXKLD-NH2
1421	Ac-WEQKITALLEQAQIQQEKNEYELQKLD-NH2
1422	Ac-WEXKITALLXQAQIQQXKNEYELXKLD-NH2
1423	Ac-XKITALLXQAQIQQXKNEYELXKLD-NH2
1425	Ac-QKITALLEQAQIQQEKNEYELQKLD-NH2
1426	Ac-QKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1427	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLD-NH2
1428	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLEN-OH
1429	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLE-OH
1430	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELL-OH
1431	Ac-VYPSDEYDASISQVNEEINQALAYIRKADEL-OH
1432	YPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1433	PSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1434	SDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1435	DEYDASISQVNEEINQALAYIRKADELLENV-NH2
1436	Ac-VYPSDEYDASISQVDEEINQALAYIRKADELLENV-NH2
1437	Ac-VYPSDEYDASISQVNEEIDQALAYIRKADELLENV-NH2
1438	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLEDV-NH2
1439	Ac-VYPSDEYDASISQVDEEIDQALAYIRKADELLENV-NH2
1440	Ac-LLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLP-NH2
1441	Ac-LSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPI-NH2
1442	Ac-STNKAVVSLSNGVSVGTSKVLDLKNYIDKQLLPIV-NH2
1443	Ac-TNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVN-NH2
1444	Ac-NKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVNK-NH2
1445	Ac-KAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVNKQ-NH2
1446	Ac-AVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVNKQS-NH2
1447	Ac-VVSLSNGVSVLTSKVDLKNYIDKQWLLPIVNKQSU-NH2
1448	Ac-VSLSNGVSVLTSKVLDLKNYIDKQLLPIVNKQSUS-NH2
1449	Ac-SLSNGVSVLTSKVLDLKNYIDKQLLPIVNKQSUSI-NH2
1450	Ac-LSNGVSVLTSKVLDKLKNYIDKQLLPIVNKQSUSIS-NH2
1451	Ac-SNGVSVLTSKVLDLKNYIDKQLLPIVNKQSUSISN-NH2
1452	Ac-NGVSVLTSKVLDLKNYIDKQLLPIVNKQSUSISNI-NH2
1453	Ac-GVSVLTSKVLDLKNYIDKQLLPIVNKQSUSISNIE-NH2
1454	Ac-VSVLTSKVLDLKNYIDKQLLPIVNKQSUSISINIET-NH2
1455	Ac-SVLTSKVLDLKNYIDKQLLPIVNKQSUSISNIETV-NH2
1456	Ac-VLTSKVLDLKNYIDKQLLPIVNKQSUSISNIETVI-NH2
1457	Ac-LTSKVLDLKNYIDKQLLPIVNKQSUSISNIETVIE-NH2
1458	Ac-TSKVLDLKNYIDKQLLPIVKQSUSISNIETVIEF-NH2
1459	Ac-SKVLDLKNYIDKQLLPIVNKQSUSISNIETVIEFQ-NH2
1460	Ac-KVLDLKNYIDKQLLPIVNKQSUSISNIETVIEFQQ-NH2
1461	Ac-VLDLKNYIDKQLLPIVNKQSUSISNIETVIEFQQK-NH2
1462	Ac-LDLKNYIDKQLLPIVNKQSUSISNIETVIEFQQKN-NH2
1463	Ac-DLKNYIDKQLLPIVNKQSUSISNIETVIEFQQKNN-NH2
1464	Ac-LKNYIDKQLLPIVNKQSUSISNIETVIEFQQKNNR-NH2
1465	Ac-KNYIDKQLLPIVNKQSUSISNIETVIEFQQKNNRL-NH2
1466	Ac-NYIDKQLLPIVNKQSUSISNIETVIEFQQKNNRLL-NH2
1467	Ac-YIDKQLLPIVNKQSUSISNIETVIEFQQKNNRLLE-NH2
1468	Ac-IDKQLLPIVNKQSUSISNIETVIEFQQKNNRLLEI-NH2
1469	Ac-DKQLLPIVNKQSUSISNIETVIEFQQKNNRLLEIT-NH2

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1470	Ac-KQLLPIVNKQSUSISNIETVIEFQQKNNRLLEITR-NH2
1471	Ac-QLLPIVNKQSUSISNIETVIEFQQKNNRLLEITRE-NH2
1472	Ac-VYPSDEYDASISQVNEEINQALA
1473	QVNEEINQALAYIRKADELLENV-NH2
1474	VYPSDEYDASISQVNEEINQALAYIRKADELLENV
1475	Ac-DEYDASISQVNEEINQALAYIREADEL-NH2
1476	Ac-DEYDASISQVNEKINQALAYIREADEL-NH2
1477	Ac-DDECLNSVKNGTYDFPKFEEESKLNRNEIKGVKLS-NH2
1478	Ac-DDE-Abu-LNSVKNGTYDFPKFEEESKLNRNEIKGVKLS-NH2
1479	Ac-YHKCDDECLNSVKNGTFDFPKFEEESKLNRNEIKGVKLSS-NH2
1480	Ac-YHK-Abu-DDE-Abu-LNSVKNGTFDFPKFEEESKLNRNEIKGVKLSS-NH2
1481	Ac-YTSLIHSLIEESQIQQEKNEQELLELDKWASLWNWF-NH2
1482	Ac-YTSLIHSLIEESQNQQEKNEYELLELDKWASLWNWF-NH2
1483	Ac-YTSLIHSLIEESQIQQEKNEYELLELDKWASLWNWF-NH2
1484	Ac-YTSLIHSLIEESQIQQEKNEYELQKLDKWASLWNWF-NH2
1485	Ac-YTSLIHSLIEESQNQQEKNEQELQKLDKWASLWNWF-NH2
1486	Ac-YTSLIHSLIEESQNQQEKNEYELQKLDKWASLWNWF-NH2
1487	Ac-YTSLIHSLIEESQIQQEKNEQELQKLDKWASLWNWF-NH2
1488	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWEWF-NH2
1489	Ac-YTSLIHSLIEESQIQQEKNEQELLELDKWASLWEWF-NH2
1490	Ac-YTSLIHSLIEESQNQQEKNEYELLELDKWASLWEWF-NH2
1491	Ac-YTSLIHSLIEESQIQQEKNEYELLELDKWASLWEWF-NH2
1492	Ac-YTSLIHSLIEESQIQQEKNEYELQKLDKWASLWEWF-NH2
1493	Ac-YTSLIHSLIEESQNQQEKNEQELQKLDKWASLWEWF-NH2
1494	Ac-YTSLIHSLIEESQNQQEKNEYELQKLDKWASLWEWF-NH2
1495	Ac-YTSLIHSLIEESQIQQEKNEQELQKLDKWASLWEWF-NH2
1496	Ac-WQEQEQKITALLEQAQIQQEKNEYELQKLDKEWWF-NH2
1497	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIEWASLWEWF-NH2
1498	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAKWASLWEWF-NH2
1499	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIKWASLWEWF-NH2
1500	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIEWAGLWEWF-NH2
1501	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAKWAGLWEWF-NH2
1502	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIKWAGLWEWF-NH2
1503	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIEWAGLWAWF-NH2
1504	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAKWAGLWAWF-NH2
1505	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIKWAGLWAWF-NH2
1506	Ac-WQEWEQKITALLEQAQIQQEKGEYELQKLDKQEQF-NH2
1507	Ac-WQEWEQKITALLEQAQIQQEKGEYELLELDKWEWF-NH2
1508	Ac-WQEWEQKITALLEQAQIQQEKGEYELQKLAKWEWF-NH2
1509	Ac-WQEWEQKITALLEQAQIQQEKGEYELQKLDWQWEF-NH2
1510	Ac-WQEWEQKITALLEQAQIQQEKGEYELLELAKWEWF-NH2
1511	Ac-WEQWEQKITALLEQAQIQQEKNEYELLELDKWEWF-NH2
1512	Ac-WQEWEQKITALLEQAQIQQEKNEYELEEELIEWASLWEWF-NH2
1513	Ac-WQEWEQKITALLEQAQIQQEKNEYELLELIEWAGLWEWF-NH2
1514	Ac-WQEWEQKITALLEQAQIQQEKNEYELLELIEWAGLWAWF-NH2
1515	Ac-WQEWEREITALLEQAQIQQEKNEYELQKLIEWASLWEWF-NH2
1516	Ac-WQEWEREIQQEKNEYELQKLDKWASLWEWF-NH2
1517	Ac-WQEWEREIQQEKGEYELQKLIEWEWF-NH2
1518	Ac-WQEWQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1519	Ac-WQEWQAQIQQEKGEYELQKLIEWEWF-NH2

T No.	Sequence
1520	PEG-GWQEWEQRITALLEQAQIQQERNEYELQRLDEWASLWEWF-NH2
1521	Ac-GWQEWEQRITALLEQAQIQQERNEYELQRLDEWASLWEWF-NH2
1522	PEG-YTSLITALLEQAQIQQERNEQELLELDEWASLWEWF-NH2
1523	Ac-YTSLITALLEQAQIQQERNEQELLELDEWASLWEWF-NH2
1526	PEG-GWQEWEQRITALLEQAQIQQERNEYELQELDEWASLWEWF-NH2
1527	Ac-GWQEWEQRITALLEQAQIQQERNEYELQELDEWASLWEWF-NH2
1528	PEG-YTSLIGSLIEESQIQQERNEQELLELDRWASLWEWF-NH2
1529	PEG-GWQEWEQRITALLEQAQIQQERNEYELQRLDRWASLWEWF-NH2
1530	Ac-GWQEWEQRITALLEQAQIQQERNEYELQRLDRWASLWEWF-NH2
1531	PEG-GWQEWEQRITALLEQAQIQQERNEYELQELDRWASLWEWF-NH2
1532	Ac-GWQEWEQRITALLEQAQIQQERNEYELQELDRWASLWEWF-NH2
1533	PEG-YTSLIGSLIEESQNQQERNEQELLELDRWASLWNWF-NH2
1534	Ac-YTSLIGSLIEESQNQQERNEQELLELDRWASLWNWF-NH2
1538	Ac-YTSLIHSLIEESQNQQEK-OH
1539	NEQELLELDK
1540	WASLWNWF-NH2
1542	Ac-AAAWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1543	Ac-WQEAAAKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1544	Ac-WQEWEQAAAALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1545	Ac-WQEWEQKITAAAEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1546	Ac-WQEWEQKITALLAAAQIQQEKNEYELQKLDKWASLWEWF-NH2
1547	Ac-WQEWEQKITALLEQAAAAQEKNEYELQKLDKWASLWEWF-NH2
1548	Ac-WQEWEQKITALLEQAQIQAAANEYELQKLDKWASLWEWF-NH2
1549	Ac-WQEWEQKITALLEQAQIQQEKAAAELQKLDKWASLWEWF-NH2
1550	Ac-WQEWEQKITALLEQAQIQQEKNEYAAAKLDKWASLWEWF-NH2
1551	Ac-WQEWEQKITALLEQAQIQQEKNEYELQAAAKWASLWEWF-NH2
1552	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDAAASLWEWF-NH
1553	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWAAAAEWF-NH
1554	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWAAA-NH
1556	Ac-YTSLIHSLIEESQNQQEKNEQELLLDKWASLWNWF-NH2
1557	Ac-YTSLIHSLIEESQNQEKNEQELLELDKWASLWNWF-NH2
1558	Ac-ERTLDFHDS-NH2
1559	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWN(W)F-NH2
1563	Ac-YTSLIHSLIEESQN(Q)QEKNEQELLELDKWASLWNWF-NH2
1564	Ac-YTSLIHSLIEESQNQQDKWASLWNWF-NH2
1566	Ac-FYEIIMDIEQNNVQGKKGIQQLQKWEDWVGWIGNI-NH2
1567	Ac-INQTIWNHGNITLGEWYNQTKDLQQKFYEIIMDIE-NH2
1568	Ac-WNHGNITLGEWYNQTKDLQQKFYEIIMDIEQNNVQ-NH2
1572	Ac-YTSLIHSLIEESENQQEKNEQELLELDKWASLWNWF-NH2
1573	Ac-YTSLIHSLIEESQDQQEKNEQELLELDKWASLWNWF-NH2
1574	Ac-YTSLIHSLIEESQNEQEKNEQELLELDKWASLWNWF-NH2
1575	c-YTSLIHSLIEESQNQEEKNEQELLELDKWASLWNWF-NH2
1576	Ac-YTSLIHSLIEESQNQQEKDEQELLELDKWASLWNWF-NH2
1577	Ac-LGEWYNQTKDLQQKFYEIIMDIEQNNVQGKKGIQQ-NH2
1578	Ac-WYNQTKDLQQKFYEIIMDIEQNNVQGKKGIQQLQK-NH2
1579	Ac-YTSLIHSLIEESQNQQEKNEEELLELDKWASLWNWF-NH2
1580	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWDWF-NH2
1586	Ac-XTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWX-NH2
1588	Ac-YNQTKDLQQKFYEIIMDIEQNNVQGKKGIQQLQKW-NH2
1598	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF

T No.	Sequence
1600	Ac-TLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQAR-NH2
1603	Ac-LQQKFYEIIMDIEQNNVQGKKGIQQLQKWEDWVGW-NH2
1627	Ac-YTSLIHSLIEESQNQQEKNEQELLALDKWASLWNWF-NH2
1628	Ac-YTSLIHSLIEESQNQQEKNEQELLEADKWASLWNWF-NH2
1629	Ac-YTSLIHSLIEESQNQQEKNEQELLELAKWASLWNWF-NH2
1630	Ac-YTSLIHSLIEESQNQQEKAEQELLELDKWASLWNWF-NH2
1631	Ac-YTSLIHSLIEESQNQQEKNAQELLELDKWASLWNWF-NH2
1632	Ac-YTSLIHSLIEESQNQQEKNEAELLELDKWASLWNWF-NH2
1634	Ac-WQEWEQKITALLEQAQIQQEKNEQELQKLDKWASLWEWF-NH2
1635	Ac-WQEWEQKITALLEQAQIQQEKAEYELQKLDKWASLWEWF-NH2
1636	Ac-WQEWEQKITALLEQAQIQQEKNAYELQKLDKWASLWEWF-NH2
1637	Ac-WQEWEQKITALLEQAQIQQEKNEAELQKLDKWASLWEWF-NH2
1644	Ac-EYDLRRWEK-NH2
1645	Ac-EQELLELDK-NH2
1646	Ac-EYELQKLDK-NH2
1647	Ac-WQEWEQKITALLEQAQIQQEKNEQELLKLDKWASLWEWF-NH2
1648	Ac-WQEWEQKITALLEQAQIQQEKNEQELLELDKWASLWEWF-NH2
1649	Ac-WQEWEQKITALLEQAQIQQEKNDKWASLWEWF-NH2
1650	Ac-YTSLIHSLIEESQNQAEKNEQELLELDKWASLWNWF-NH2
1651	Ac-YTSLIHSLIEESQNQQAKNEQELLELDKWASLWNWF-NH2
1652	Ac-YTSLIHSLIEESQNQQEANEQELLELDKWASLWNWF-NH2
1653	Ac-YTSLIHSLIEESANQQEANEQELLELDKWASLWNWF-NH2
1654	Ac-YTSLIHSLIEESQAQQEKNEQELLELDKWASLWNWF-NH2
1655	Ac-YTSLIHSLIEESQNAQEKNEQELLELDKWASLWNWF-NH2
1656	Ac-YTSLIHALIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1657	Ac-YTSLIHSAIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1658	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1659	Ac-YTSLIHSLAEESQNQQEKNEQELLELDKWASLWNWF-NH2
1660	Ac-YTSAIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1661	Ac-YTSLAHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1662	Ac-YTSLIASLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1663	Ac-ATSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1664	Ac-YASLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1665	Ac-YTALIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1666	Ac-RIQDLEKYVEDTKIDLWSYNAELLVALENQ-NH2
1667	Ac-HTIDLTDSEMNKLFEKTRRQLREN-NH2
1668	Ac-SEMNKLFEKTRRQLREN -NH2
1669	Ac-VFPSDEADASISQVNEKINQSLAFIRKSDELLHNV-NH2
1670	Ac-VFPSDEFAASISQVNEKINQSLAFIRKSDELLHNV-NH2
1671	Ac-VFPSDEFDASISAVNEKINQSLAFIRKSDELLHNV-NH2
1672	Ac-VFPSDEFDASISQANEKINQSLAFIRKSDELLHNV-NH2
1673	Ac-VFPSDEFDASISQVAEKINQSLAFIRKSDELLHNV-NH2
1674	Ac-WQEWEQKITAALEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1675	Ac-WQEWEQKITALAEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1676	Ac-WQEWEQKITALLEQAAIQQEKNEYELQKLDKWASLWEWF-NH2
1677	Ac-WQEWEQKITALLEQAQAQQEKNEYELQKLDKWASLWEWF-NH2
1678	Ac-WQEWEQKITALLEQAQIAQEKNEYELQKLDKWASLWEWF-NH2
1679	Ac-WQEWEQKITALLEQAQIQAEKNEYELQKLDKWASLWEWF-NH2
1680	Ac-VFPSDEFDASISQVNEKINQSAAFIRKSDELLHNV-NH2
1681	Ac-VFPSDEFDASISQVNEKINQSLAAIRKSDELLHNV-NH2

T No.	Sequence
1682	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDEALHNV-NH2
1683	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELAHNV-NH2
1684	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLANV-NH2
1685	Ac-WQEWEQKITALLEQAQIQQAKNEYELQKLDKWASLWEWF-NH2
1687	Ac-WQEWEQKITALLEQAQIQQEKNEYELQALDKWASLWEWF-NH2
1688	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKADKWASLWEWF-NH2

5.4. SYNTHESIS OF PEPTIDES

The peptides of the invention may be synthesized or prepared by techniques well known in the art. See, for example, Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman and Co., NY, which is incorporated herein by reference in its entirety. Short peptides, for example, can be synthesized on a solid support or in solution. Longer peptides may be made using recombinant DNA techniques. Here, the nucleotide sequences encoding the peptides of the invention may be synthesized, and/or cloned, and expressed according to techniques well known to those of ordinary skill in the art. See, for example, Sambrook, et al., 1989, Molecular Cloning, A Laboratory Manual, Vols. 1-3, Cold Spring Harbor Press, NY.

The peptides of the invention may alternatively be synthesized such that one or more of the bonds which link the amino acid residues of the peptides are non-peptide bonds. These alternative non-peptide bonds may be formed by utilizing reactions well known to those in the art, and may include, but are not limited to imino, ester, hydrazide, semicarbazide, and azo bonds, to name but a few. In yet another embodiment of the invention, peptides comprising the sequences described above may be synthesized with additional chemical groups present at their amino and/or carboxy termini, such that, for example, the stability, bioavailability, and/or inhibitory activity of the peptides is enhanced. For example, hydrophobic groups such as carbobenzoxyl, dansyl, or t-butyloxycarbonyl groups, may be added to the peptides' amino termini. Likewise, an acetyl group or a 9-fluorenylmethoxy-carbonyl group may be placed at the

peptides' amino termini. (See "X" Tables I to IV, above.) Additionally, the hydrophobic group, t-butyloxycarbonyl, or an amido group may be added to the peptides' carboxy termini. (See "Z" in Tables I to IV, above.)

Further, the peptides of the invention may be synthesized such that their steric configuration is altered. For example, the D-isomer of one or more of the amino acid residues of the peptide may be used, rather than the usual L-isomer.

Still further, at least one of the amino acid residues of the peptides of the invention may be substituted by one of the well known non-naturally occurring amino acid residues. Alterations such as these may serve to increase the stability, bioavailability and/or inhibitory action of the peptides of the invention.

Any of the peptides described above may, additionally, have a macromolecular carrier group covalently attached to their amino and/or carboxy termini. Such macromolecular carrier groups may include, for example, lipid-fatty acid conjugates, polyethylene glycol, carbohydrates or additional peptides. "X", in Tables I to IV, above, may therefore additionally represent any of the above macromolecular carrier groups covalently attached to the amino terminus of a peptide, with an additional peptide group being preferred. Likewise, "Z", in Tables I to IV, may additionally represent any of the macromolecular carrier groups described above.

5.5. ASSAYS FOR ANTI-MEMBRANE FUSION ACTIVITY

Described herein, are methods for ability of a compound, such as the peptides of the invention, to

inhibit membrane fusion events. Specifically, assays for cell fusion events are described in Section 5.5.1, below, and assays for antiviral activity are described in Section 5.5.2, below.

5.5.1 ASSAYS FOR CELL FUSION EVENTS

Assays for cell fusion events are well known to those of skill in the art, and may be used in conjunction, for example, with the peptides of the invention to test the peptides' antifusogenic capabilities.

Cell fusion assays are generally performed in vitro. Such an assay may comprise culturing cells which, in the absence of any treatment would undergo an observable level of syncytial formation. For example, uninfected cells may be incubated in the presence of cells chronically infected with a virus that induces cell fusion. Such viruses may include, but are not limited to, HIV, SIV, or respiratory syncytial virus.

For the assay, cells are incubated in the presence of a peptide to be assayed. For each peptide, a range of peptide concentrations may be tested. This range should include a control culture wherein no peptide has been added.

Standard conditions for culturing cells, well known to those of ordinary skill in the art, are used. After incubation for an appropriate period (24 hours at 37°C, for example) the culture is examined microscopically for the presence of multinucleated giant cells, which are indicative of cell fusion and syncytial formation. Well known stains, such as crystal violet stain, may be used to facilitate the visualization of syncytial formation.

5.5.2 ASSAYS FOR ANTIVIRAL ACTIVITY

The antiviral activity exhibited by the peptides of the invention may be measured, for example, by easily performed in vitro assays, such as those described below, which can test the peptides' ability to inhibit syncytia formation, or their ability to inhibit infection by cell-free virus. Using these assays, such parameters as the relative antiviral activity of the peptides, exhibit against a given strain of virus and/or the strain specific inhibitory activity of the peptide can be determined.

A cell fusion assay may be utilized to test the peptides' ability to inhibit viral-induced, such as HIV-induced, syncytia formation in vitro. Such an assay may comprise culturing uninfected cells in the presence of cells chronically infected with a syncytial-inducing virus and a peptide to be assayed. For each peptide, a range of peptide concentrations may be tested. This range should include a control culture wherein no peptide has been added. Standard conditions for culturing, well known to those of ordinary skill in the art, are used. After incubation for an appropriate period (24 hours at 37°C, for example) the culture is examined microscopically for the presence of multinucleated giant cells, which are indicative of cell fusion and syncytia formation. Well known stains, such as crystal violet stain, may be used to facilitate syncytial visualization. Taking HIV as an example, such an assay would comprise CD-4$^+$ cells (such as Molt or CEM cells, for example) cultured in the presence of chronically HIV-infected cells and a peptide to be assayed.

Other well known characteristics of viral infection may also be assayed to test a peptide's

antiviral capabilities. Once again taking HIV as an example, a reverse transcriptase (RT) assay may be utilized to test the peptides' ability to inhibit infection of CD-4+ cells by cell-free HIV. Such an assay may comprise culturing an appropriate concentration (i.e., $TCID_{50}$) of virus and CD-4+ cells in the presence of the peptide to be tested. Culture conditions well known to those in the art are used. As above, a range of peptide concentrations may be used, in addition to a control culture wherein no peptide has been added. After incubation for an appropriate period (e.g., 7 days) of culturing, a cell-free supernatant is prepared, using standard procedures, and tested for the present of RT activity as a measure of successful infection. The RT activity may be tested using standard techniques such as those described by, for example, Goff et al. (Goff, S. et al., 1981, J. Virol. 38:239-248) and/or Willey et al. (Willey, R. et al., 1988, J. Virol. 62:139-147). These references are incorporated herein by reference in their entirety.

Standard methods which are well-known to those of skill in the art may be utilized for assaying non-retroviral activity. See, for example, Pringle et al. (Pringle, C.R. et al., 1985, J. Medical Virology 17:377-386) for a discussion of respiratory syncytial virus and parainfluenza virus activity assay techniques. Further, see, for example, "Zinsser Microbiology", 1988, Joklik, W.K. et al., eds., Appleton & Lange, Norwalk, CT, 19th ed., for a general review of such techniques. These references are incorporated by reference herein in their entirety. In addition, the Examples presented below, in Sections

17, 18, 26 and 27 each provide additional assays for the testing of a compound's antiviral capability.

In vivo assays may also be utilized to test, for example, the antiviral activity of the peptides of the invention. To test for anti-HIV activity, for example, the in vivo model described in Barnett et al. (Barnett, S.W. et al., 1994, Science 266:642-646) may be used.

Additionally, anti-RSV activity can be assayed in vivo via well known mouse models. For example, RSV can be administered intranasally to mice of various inbred strains. Virus replicates in lungs of all strains, but the highest titers are obtained in P/N, C57L/N and DBA/2N mice. Infection of BALB/c mice produces an asymptomatic bronchiolitis characterized by lymphocytic infiltrates and pulmonary virus titers of 10^4 to 10^5 pfu/g of lung tissue (Taylor, G. et al., 1984, Infect. Immun. 43:649-655).

Cotton rat models of RSV are also well known. Virus replicates to high titer in the nose and lungs of the cotton rat but produces few if any signs of inflammation.

5.6. USES OF THE PEPTIDES OF THE INVENTION

The peptides of the invention may be utilized as antifusogenic or antiviral compounds, or as compounds which modulate intracellular processes involving coiled coil peptide structures. Further, such peptides may be used to identify agents which exhibit antifusogenic, antiviral or intracellular modulatory activity. Still further, the peptides of the invention may be utilized as organism or viral type/subtype-specific diagnostic tools.

The antifusogenic capability of the peptides of the invention may additionally be utilized to inhibit or treat/ameliorate symptoms caused by processes involving membrane fusion events. Such events may include, for example, virus transmission via cell-cell fusion, abnormal neurotransmitter exchange via cell-fusion, and sperm-egg fusion. Further, the peptides of the invention may be used to inhibit free viral, such as retroviral, particularly HIV, transmission to uninfected cells wherein such viral infection involves membrane fusion events or involves fusion of a viral structure with a cell membrane. Among the intracellular disorders involving coiled coil peptides structures which may be ameliorated by the peptides of the invention are disorders involving, for example, bacterial toxins.

With respect to antiviral activity, the viruses whose transmission may be inhibited by the peptides of the invention include, but are not limited to human retroviruses, such as HIV-1 and HIV-2 and the human T-lymphocyte viruses (HTLV-I and II), and non-human retroviruses such as bovine leukosis virus, feline sarcoma and leukemia viruses, simian immunodeficiency, sarcoma and leukemia viruses, and sheep progress pneumonia viruses.

Non retroviral viruses whose transmission may be inhibited by the peptides of the invention include, but are not limited to human respiratory syncytial virus, canine distemper virus, newcastle disease virus, human parainfluenza virus, influenza viruses, measles viruses, Epstein-Barr viruses, hepatitis B viruses, and simian Mason-Pfizer viruses.

Non enveloped viruses whose transmission may be inhibited by the peptides of the invention include,

but are not limited to picornaviruses such as polio viruses, hepatitis A virus, enterovirus, echoviruses and coxsackie viruses, papovaviruses such as papilloma virus, parvoviruses, adenoviruses and reoviruses.

As discussed more fully, below, in Section 5.6.1 and in the Example presented, below, in Section 8, DP107, DP178, DP107 analog and DP178 analog peptides form non-covalent protein-protein interactions which are required for normal activity of the virus. Thus, the peptides of the invention may also be utilized as components in assays for the identification of compounds that interfere with such protein-protein interactions and may, therefore, act as antiviral agents. These assays are discussed, below, in Section 5.6.1.

As demonstrated in the Example presented below in Section 6, the antiviral activity of the peptides of the invention may show a pronounced type and subtype specificity, i.e., specific peptides may be effective in inhibiting the activity of only specific viruses. This feature of the invention presents many advantages. One such advantage, for example, lies in the field of diagnostics, wherein one can use the antiviral specificity of the peptide of the invention to ascertain the identity of a viral isolate. With respect to HIV, one may easily determine whether a viral isolate consists of an HIV-1 or HIV-2 strain. For example, uninfected CD-4$^+$ cells may be co-infected with an isolate which has been identified as containing HIV the DP178 (SEQ ID:1) peptide, after which the retroviral activity of cell supernatants may be assayed, using, for example, the techniques described above in Section 5.2. Those isolates whose retroviral activity is completely or nearly completely

inhibited contain HIV-1. Those isolates whose viral activity is unchanged or only reduced by a small amount, may be considered to not contain HIV-1. Such an isolate may then be treated with one or more of the other DP178 peptides of the invention, and subsequently be tested for its viral activity in order to determine the identify of the viral isolate. The DP107 and DP178 analogs of the invention may also be utilized in a diagnostic capacity specific to the type and subtype of virus or organism in which the specific peptide sequence is found. A diagnostic procedure as described, above, for DP178, may be used in conjunction with the DP107/DP178 analog of interest.

5.6.1. SCREENING ASSAYS

As demonstrated in the Example presented in Section 8, below, DP107 and DP178 portions of the TM protein gp41, *i.e.*, the HR1 and HR2 portions of gp41, respectively, form non-covalent protein-protein interactions. As is also demonstrated, the maintenance of such interactions is necessary for normal viral infectivity. Thus, compounds which bind DP107, bind DP178, and/or act to disrupt normal DP107/DP178 protein-protein interactions may act as antifusogenic, antiviral or cellular modulatory agents. Described below are assays for the identification of such compounds. Note that, while, for ease and clarity of discussion, DP107 and DP178 peptides will be used as components of the assays described, but it is to be understood that any of the DP107 analog or DP178 analog peptides described, above, in Sections 5.1 through 5.3 may also be utilized as part of these screens for compounds.

For example, in certain embodiments the assays of the invention may be use DP107 and/or DP178 analogs that contain one or more amino acid residue truncations, deletions, insertions or substitutions. In particular, in one preferred embodiment, the DP107, DP178, DP107-like and DP178-like peptides can comprise amino and/or carboxy-terminal insertions corresponding to about two to about fifty amino acids amino-to or carboxy-to the endogenous sequence from which the DP107, DP178, DP107-like or DP178-like peptide is derived. In another particular embodiment, the peptides used in the assays described herein further comprise additional, heterologous sequence useful for detecting, immobilizing and/or purifying the particular peptide. Such heterologous sequences include, but are not limited to maltose binding fusion proteins containing a DP178, DP107, DP178-like or DP107-like sequence such as the M41Δ178 and MF5.1 maltose binding fusion proteins described in Sections 8 and 30, below.

In certain embodiments, such analogs will have reduced binding affinities and are therefore useful, *e.g.*, to screen for compounds which inhibit the formation of or, alternatively, disrupt complexes between DP107/DP178 complexes. Among such reduced binding analogs are peptides exhibiting one or more alanine insertion or substitutions, including, *e.g.*, the peptides described in the examples presented in Sections 30 and 31, below. It is understood that such analogs which have reduced binding affinities, including the analogs described in Sections 30 and 31 below, are also part of the present invention.

Compounds which may be tested for an ability to bind DP107, DP178, and/or disrupt DP107/DP178 interactions, and which therefore, potentially represent antifusogenic, antiviral or intracellular modulatory compounds, include, but are not limited to, peptides made of D- and/or L-configuration amino acids (in, for example, the form of random peptide libraries; see Lam, K.S. et al., 1991, Nature 354:82-84), phosphopeptides (in, for example, the form of random or partially degenerate, directed phosphopeptide libraries; see, for example, Songyang, Z. et al., 1993, Cell 72:767-778), antibodies, and small organic or inorganic molecules. Synthetic compounds, natural products, and other sources of potentially effective materials may be screened in a variety of ways, as described in this Section.

Compounds that can be screened, tested and identified as modulating HR1/HR2, DP178/DP107 and/or DP178-like/DP107-like interactions utilizing the methods described herein can, in general, include, *e.g.*, small molecules that are of a molecular weight up to about 1500 daltons. Test compounds, including small molecules, can include, but are not limited to, compounds obtained from any commercial source, including Aldrich (1001 West St. Paul Ave., Milwaukee, WI 53233), Sigma Chemical (P.O. Box 14508, St. Louis, MO 63178), Fluka Chemie AG (Industriestrasse 25, CH-9471 Buchs, Switzerland (Fluka Chemical Corp. 980 South 2nd Street, Ronkonkoma, NY 11779)), Eastman Chemical Company, Fine Chemicals (P.O Box 431, Kingsport, TN 37662), Boehringer Mannheim GmbH (Sandhofer Strasse 116, D-68298 Mannheim), Takasago (4 Volvo Drive, Rockleigh, NJ 07647), SST Corporation

(635 Brighton Road, Clifton, NJ 07012), Ferro (111 West Irene Road, Zachary, LA 70791), Riedel-deHaen Aktiengesellschaft (P.O. Box D-30918, Seelze, Germany), PPG Industries Inc., Fine Chemicals (One PPG Place, 34th Floor, Pittsburgh, PA 15272). Further any kind of natural products may be screened using the methods of the invention, including microbial, fungal or plant extracts.

Furthermore, diversity libraries of test compounds, including small molecule test compounds, may be commercially obtained from Specs and BioSpecs B.V. (Rijswijk, The Netherlands), Chembridge Corporation (San Diego, CA), Contract Service Company (Dolgoprudny, Moscow Region, Russia), Comgenex USA Inc. (Princeton, NJ), Maybridge Chemicals Ltd. (Cornwall PL34 OHW, United Kingdom), and Asinex (Moscow, Russia). Combinatorial libraries of test compounds, including small molecule test compounds, can be may be generated as disclosed in Eichler & Houghten, 1995, *Mol. Med. Today* 1:174-180; Dolle, 1997, *Mol. Divers.* 2:223-236; Lam, 1997, *Anticancer Drug Des.* 12:145-167. These references are incorporated hereby by reference in their entirety. It is to be noted that such references also teach additional screening methods which may be employed for the further testing of compounds identified via the methods of the invention and which can aid in identifying and isolating compounds which can represent leads and therapeutic compounds.

The compounds, antibodies, or other molecules identified may be tested, for example, for an ability to inhibit cell fusion or viral activity, utilizing, for example, assays such as those described, above, in Section 5.5.

Among the peptides which may be tested are soluble peptides comprising DP107 and/or DP178 domains, and peptides comprising DP107 and/or DP178 domains having one or more mutations within one or both of the domains, such as the M41-P peptide described, below, in the Example presented in Section 8, which contains a isoleucine to proline mutation within the DP178 sequence.

In one embodiment of such screening methods is a method for identifying a compound to be tested for antiviral ability comprising:

1 exposing at least one compound to a peptide comprising a DP107 peptide for a time sufficient to allow binding of the compound to the DP107 peptide;

2 removing non-bound compounds; and

3 determining the presence of the compound bound to the DP107 peptide,

thereby identifying an agent to be tested for antiviral ability.

In a second embodiment of such screening methods is a method for identifying a compound to be tested for antiviral ability comprising:

(a) exposing at least one compound to a peptide comprising a DP178 peptide for a time sufficient to allow binding of the compound to the DP178 peptide;

(b) removing non-bound compounds; and

(c) determining the presence of the compound bound to the DP178 peptide, thereby identifying an agent to be tested for antiviral ability.

One method utilizing these types of approaches that may be pursued in the isolation of such DP107-binding or DP178-binding compounds is an assay which would include the attachment of either the DP107 or the DP178 peptide to a solid matrix, such as, for example, agarose or plastic beads, microtiter plate wells, petri dishes, or membranes composed of, for example, nylon or nitrocellulose. In such an assay system, either the DP107 or DP178 protein may be anchored onto a solid surface, and the compound, or test substance, which is not anchored, is labeled, either directly or indirectly (*e.g.*, with a radioactive label such as ^{125}I, an absorption label such as biotin, or a fluorescent label such as fluorescein or rhodamine). In practice, microtiter plates are conveniently utilized. The anchored component may be immobilized by non-covalent or covalent attachments. Non-covalent attachment may be accomplished simply by coating the solid surface with a solution of the protein and drying. Alternatively, an immobilized antibody, preferably a monoclonal antibody, specific for the protein may be used to anchor the protein to the solid surface. The surfaces may be prepared in advance and stored.

In order to conduct the assay, the labeled compound is added to the coated surface containing the anchored DP107 or DP178 peptide. After the reaction is complete, unreacted components are removed (e.g., by washing) under conditions such that any complexes

formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the compound is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the labeled component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; e.g., using a labeled antibody specific for the compound (the antibody, in turn, may be directly labeled or indirectly labeled with a labeled anti-Ig antibody).

Alternatively, such an assay can be conducted in a liquid phase, the reaction products separated from unreacted components, and complexes detected; e.g., using an immobilized antibody specific for DP107 or DP178, whichever is appropriate for the given assay, or ab antibody specific for the compound, i.e., the test substance, in order to anchor any complexes formed in solution, and a labeled antibody specific for the other member of the complex to detect anchored complexes.

By utilizing procedures such as this, large numbers of types of molecules may be simultaneously screened for DP107 or DP178-binding capability, and thus potential antiviral activity.

Further, compounds may be screened for an ability to inhibit the formation of or, alternatively, disrupt DP107/DP178 complexes. Such compounds may then be tested for antifusogenic, antiviral or intercellular modulatory capability. For ease of description, DP107 and DP178 will be referred to as "binding partners." Compounds that disrupt such interactions may exhibit antiviral activity. Such compounds may include, but

are not limited to molecules such as antibodies, peptides, and the like described above.

The basic principle of the assay systems used to identify compounds that interfere with the interaction between the DP107 and DP178 peptides involves preparing a reaction mixture containing peptides under conditions and for a time sufficient to allow the two peptides to interact and bind, thus forming a complex. In order to test a compound for disruptive activity, the reaction is conducted in the presence and absence of the test compound, i.e., the test compound may be initially included in the reaction mixture, or added at a time subsequent to the addition of one of the binding partners; controls are incubated without the test compound or with a placebo. The formation of any complexes between the binding partners is then detected. The formation of a complex in the control reaction, but not in the reaction mixture containing the test compound indicates that the compound interferes with the interaction of the DP107 and DP178 peptides.

The assay for compounds that interfere with the interaction of the binding partners can be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring one of the binding partners onto a solid phase and detecting complexes anchored on the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested. For example, test compounds that interfere with the interaction between the binding partners, e.g., by competition, can be

identified by conducting the reaction in the presence of the test substance; i.e., by adding the test substance to the reaction mixture prior to or simultaneously with the binding partners. On the other hand, test compounds that disrupt preformed complexes, e.g. compounds with higher binding constants that displace one of the binding partners from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are described briefly below.

In a heterogeneous assay system, one binding partner, e.g., either the DP107 or DP178 peptide, is anchored onto a solid surface, and its binding partner, which is not anchored, is labeled, either directly or indirectly (*e.g.*, with a radioactive label such as ^{125}I, an absorption label such as biotin, or a fluorescent label such as fluorescein or rhodamine). In practice, microtiter plates are conveniently utilized. The anchored species may be immobilized by non-covalent or covalent attachments. Non-covalent attachment may be accomplished simply by coating the solid surface with a solution of the protein and drying. Alternatively, an immobilized antibody specific for the protein may be used to anchor the protein to the solid surface. The surfaces may be prepared in advance and stored.

In order to conduct the assay, the binding partner of the immobilized species is added to the coated surface with or without the test compound. After the reaction is complete, unreacted components are removed (e.g., by washing) and any complexes formed will remain immobilized on the solid surface.

The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the binding partner was pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the binding partner is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; e.g., using a labeled antibody specific for the binding partner (the antibody, in turn, may be directly labeled or indirectly labeled with a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which inhibit complex formation or which disrupt preformed complexes can be detected.

Alternatively, the reaction can be conducted in a liquid phase in the presence or absence of the test compound, the reaction products separated from unreacted components, and complexes detected; e.g., using an immobilized antibody specific for one binding partner to anchor any complexes formed in solution, and a labeled antibody specific for the other binding partner to detect anchored complexes. Again, depending upon the order of addition of reactants to the liquid phase, test compounds which inhibit complex or which disrupt preformed complexes can be identified.

In an alternate embodiment of the invention, a homogeneous assay can be used. In this approach, a preformed complex of the DP107 and DP178 peptides is prepared in which one of the binding partners is labeled, but the signal generated by the label is quenched due to complex formation (see, e.g., U.S. Patent No. 4,109,496 by Rubenstein which utilizes this approach for immunoassays). The addition of a test

substance that competes with and displaces one of the binding partners from the preformed complex will result in the generation of a signal above background. In this way, test substances which disrupt DP-107/DP-178 protein-protein interaction can be identified.

In still another embodiment of the invention, fluorescence polarization may be used in a homogenous assay. In this approach, complex formation is detected by measuring the polarization of a fluorescently labeled peptide (*e.g.*, with fluorescein or rhodamine) in a sample. Binding of the peptide to its complementary HR1 or HR2 binding domain in a larger molecular weight peptide or protein, such as in a maltose binding fusion protein described herein, alters the correlation time of the fluorescent moiety and thereby decreases the fluroescence polarization of the labeled peptide.

In an alternative screening assay, test compounds may be assayed for the their ability to disrupt a DP178/DP107 interaction, as measured immunometrically using an antibody specifically reactive to a DP107/DP178 complex (i.e., an antibody that recognizes neither DP107 nor DP178 individually). Such an assay acts as a competition assay, and is based on techniques well known to those of skill in the art.

The above competition assay may be described, by way of example, and not by way of limitation, by using the DP178 and M41Δ178 peptides and by assaying test compounds for the disruption of the complexes formed by these two peptides by immunometrically visualizing DP178/M41Δ178 complexes via the human recombinant Fab, Fab-d, as described, below, in the Example presented in Section 8. M41Δ178 is a maltose binding fusion

protein containing a gp41 region having its DP178 domain deleted, and is described, below, in the Example presented in Section 8.

Utilizing such an assay, M41Δ178 may be immobilized onto solid supports such as microtiter wells. A series of dilutions of a test compound may then be added to each M41Δ178-containing well in the presence of a constant concentration of DP-178 peptide. After incubation, at, for example, room temperature for one hour, unbound DP-178 and test compound are removed from the wells and wells are then incubated with the DP178/M41Δ178-specific Fab-d antibody. After incubation and washing, unbound Fab-d is removed from the plates and bound Fab-d is quantitated. A no-inhibitor control should also be conducted. Test compounds showing an ability to disrupt DP178/M41Δ178 complex formation are identified by their concentration-dependent decrease in the level of Fab-d binding.

A variation of such an assay may be utilized to perform a rapid, high-throughput binding assay which is capable of directly measuring DP178 binding to M41Δ178 for the determination of binding constants of the ligand of inhibitory constants for competitors of DP178 binding.

Such an assay takes advantage of accepted radioligand and receptor binding principles. (See, for example, Yamamura, H.I. et al., 1985, "Neurotransmitter Receptor Binding", 2nd ed., Raven Press, NY.) As above, M41Δ178 is immobilized onto a solid support such as a microtiter well. DP178 binding to M41Δ178 is then quantitated by measuring the fraction of DP178 that is bound as ^{125}I-DP178 and calculating the total amount bound using a value for

specific activity (dpm/μg peptide) determined for each labeled DP178 preparation. Specific binding to M41Δ178 is defined as the difference of the binding of the labeled DP178 preparation in the microtiter wells (totals) and the binding in identical wells containing, in addition, excess unlabeled DP178 (nonspecifics).

Because the binding affinity for native DP178 and DP107 is very high (including native DP178-like and DP107-like peptides from other species; *e.g.*, 10 nM for DP178 in HIV-1, and 2 nM for T112 in RSV), test compounds must exhibit high binding properties to interfere with or disrupt the DP178/DP107 binding interaction. Accordingly, in another non-limiting example of the above-described competitions assays, such assays can be performed using "modified" DP107 and/or DP178 peptides (*e.g.*, DP107 and/or DP178 analogs) which have reduced binding affinities relatived to the unmodified "parent peptides". The use of such modified DP107 and DP178 peptides greatly increases the sensitivity of the competition assays of the invention by identifying more compounds with inhibitory potential. The binding affinities of compounds identified in the assays can then be optimized, *e.g.*, using standard medicinal chemistry techniques, to generate compounds that are more powerful inhibitors of DP107/DP178 complex formation and are therefore useful, *e.g.*, as antiviral reagents. Alternatively, compounds identified in the competition assays using DP107 and/or DP178 analogs with reduced binding affinities may, themselves, be useful, *e.g.*, as antiviral reagents.

The term "reduced affinity," as used herein, refers to a DP107, DP178, DP107-like or DP178-like peptide that interacts with and forms a DP107/DP178 peptide pair, a HR1/DP178 pair or an HR2/DP107 pair under competition assay conditions, but interacts with its "partner" to form such a pair with a lower affinity than would a DP107 or DP178 "parent" peptide from which the reduced affinity peptide is derived.

Generally, the binding affinity of a peptide can be expressed as a B_{50} value, *i.e.*, the concentration of peptide necessary for 50% of the peptide molecules to bind to their target under a given set of conditions. Preferably, the B_{50} value of a reduced affinity peptide will by at least twice, and more preferably at least five times, at least 10 times, at least 20 times, or at least 100 times the B_{50} value of the unmodified peptide from which it was derived.

Modified DP107 and DP178 peptides that have reduced binding affinities may be generated according to any number of techniques that will be readily apparent to those skilled in the art. For example, in one embodiment modified DP107 and DP178 peptides with reduced binding affinities may be generated by generating truncated DP107 and DP178 peptides, respectively. Such peptides may be routinely synthesized and tested, *e.g.*, by the above described screening assays, to determine their binding affinities to their target. For example, as described in the example presented below in Section 30, reducing the length of the native RSV DP178-like peptide T112 from 35 to 28 amino acid residues resulted in a five fold drop in binding affinity (from 1 nM to 5 nM).

Generally, such truncation can be of 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid residues.

Alternatively, modified DP107 and DP178 peptides with reduced binding affinity may be identified and generated by identifying and substituting, inserting or deleting amino acid residues. For example in one embodiment, which is also demonstrated in the example presented below in Section 30, modified DP107 and/or DP178 peptides may be routinely synthesized and assayed for reduced binding affinity by systematically replacing one or more amino acid residues of the native DP107 or DP178 peptide with other amino acid residues and testing the binding affinity of the resulting peptide by techniques such as those described herein. Preferably, the substituted amino acid residues are neutral amino acid residues exhibiting relatively small side chains, such as alanine or glycine.

Such substitutions can identify "key" amino acid residues and can be used in the competition assays of the invention. Alternatively, upon identification of key residues by such systematic substitutions, the key residues can be changed to other residues and the resulting, modified peptides can be tested for binding affinity.

Modified DP107 and/or DP178 peptides that have reduced binding affinities may still further be identified using principles of protein chemistry and design that are well known to those of skill in the art. Specifically, such principles may be used to identify those amino acid residues of a native DP107 or DP178 sequence that effect, *e.g.*, solubility, binding affinity, or stability of the peptide. Thus,

for example, using known principles of amino acid chemistry and protein design one skilled in the art could identify amino acid residues in a native DP107 or DP178 peptide that affect the structure of the peptide.

5.7 PHARMACEUTICAL FORMULATIONS, DOSAGES AND MODES OF ADMINISTRATION

The peptides of the invention may be administered using techniques well known to those in the art. Preferably, agents are formulated and administered systemically. Techniques for formulation and administration may be found in "Remington's Pharmaceutical Sciences", 18th ed., 1990, Mack Publishing Co., Easton, PA. Suitable routes may include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as, intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections, just to name a few. For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

In instances wherein intracellular administration of the peptides of the invention or other inhibitory agents is preferred, techniques well known to those of ordinary skill in the art may be utilized. For example, such agents may be encapsulated into

liposomes, then administered as described above. Liposomes are spherical lipid bilayers with aqueous interiors. All molecules present in an aqueous solution at the time of liposome formation are incorporated into the aqueous interior. The liposomal contents are both protected from the external microenvironment and, because liposomes fuse with cell membranes, are effectively delivered into the cell cytoplasm. Additionally, due to their hydrophobicity, when small molecules are to be administered, direct intracellular administration may be achieved.

Nucleotide sequences encoding the peptides of the invention which are to be intracellularly administered may be expressed in cells of interest, using techniques well known to those of skill in the art. For example, expression vectors derived from viruses such as retroviruses, vaccinia viruses, adeno-associated viruses, herpes viruses, or bovine papilloma viruses, may be used for delivery and expression of such nucleotide sequences into the targeted cell population. Methods for the construction of such vectors and expression constructs are well known. See, for example, Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Cold Spring Harbor NY, and Ausubel et al., 1989, Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley Interscience, NY.

With respect to HIV, peptides of the invention, particularly DP107 and DP178, may be used as therapeutics in the treatment of AIDS. In addition, the peptides may be used as prophylactic measures in previously uninfected individuals after acute exposure to an HIV virus. Examples of such prophylactic use of

the peptides may include, but are not limited to, prevention of virus transmission from mother to infant and other settings where the likelihood of HIV transmission exists, such as, for example, accidents in health care settings wherein workers are exposed to HIV-containing blood products. The successful use of such treatments do not rely upon the generation of a host immune response directed against such peptides.

Effective dosages of the peptides of the invention to be administered may be determined through procedures well known to those in the art which address such parameters as biological half-life, bioavailability, and toxicity. Given the data presented below in Section 6, DP178, for example, may prove efficacious in vivo at doses required to achieve circulating levels of about 1 to about 10 ng per ml of peptide.

A therapeutically effective dose refers to that amount of the compound sufficient to result in amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. Compounds which exhibit large therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of

circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} (e.g., the concentration of the test compound which achieves a half-maximal inhibition of the fusogenic event, such as a half-maximal inhibition of viral infection relative to the amount of the event in the absence of the test compound) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography (HPLC).

The peptides of the invention may, further, serve the role of a prophylactic vaccine, wherein the host raises antibodies against the peptides of the invention, which then serve to neutralize HIV viruses by, for example, inhibiting further HIV infection.

Administration of the peptides of the invention as a prophylactic vaccine, therefore, would comprise administering to a host a concentration of peptides effective in raising an immune response which is sufficient to neutralize HIV, by, for example, inhibiting HIV ability to infect cells. The exact concentration will depend upon the specific peptide to be administered, but may be determined by using standard techniques for assaying the development of an immune response which are well known to those of

ordinary skill in the art. The peptides to be used as vaccines are usually administered intramuscularly.

The peptides may be formulated with a suitable adjuvant in order to enhance the immunological response. Such adjuvants may include, but are not limited to mineral gels such as aluminum hydroxide; surface active substances such as lysolecithin, pluronic polyols, polyanions; other peptides; oil emulsions; and potentially useful human adjuvants such as BCG and Corynebacterium parvum. Many methods may be used to introduce the vaccine formulations described here. These methods include but are not limited to oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, and intranasal routes.

Alternatively, an effective concentration of polyclonal or monoclonal antibodies raised against the peptides of the invention may be administered to a host so that no uninfected cells become infected by HIV. The exact concentration of such antibodies will vary according to each specific antibody preparation, but may be determined using standard techniques well known to those of ordinary skill in the art. Administration of the antibodies may be accomplished using a variety of techniques, including, but not limited to those described in this section.

For all such treatments described above, the exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g. Fingl et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p1).

It should be noted that the attending physician would know how to and when to terminate, interrupt, or

adjust administration due to toxicity, or to organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administrated dose in the management of the oncogenic disorder of interest will vary with the severity of the condition to be treated and the route of administration. The dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the invention. With proper choice of carrier and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability

of those skilled in the art, especially in light of the detailed disclosure provided herein.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipient, optionally grinding a resulting mixture,

and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

6. EXAMPLE: DP178 (SEQ ID:1) IS A POTENT INHIBITOR OF HIV-1 INFECTION

In this example, DP178 (SEQ ID:1) is shown to be a potent inhibitor of HIV-1 mediated CD-4$^+$ cell-cell fusion and infection by cell free virus. In the fusion assay, this peptide completely blocks virus induced syncytia formation at concentrations of from 1-10 ng/ml. In the infectivity assay the inhibitory concentration is somewhat higher, blocking infection at 90ng/ml. It is further shown that DP178 (SEQ ID:1) shows that the antiviral activity of DP178 (SEQ ID:1) is highly specific for HIV-1. Additionally, a synthetic peptide, DP-185 (SEQ ID:3), representing a HIV-1-derived DP178 homolog is also found to block HIV-1-mediated syncytia formation.

6.1. MATERIALS AND METHODS

6.1.1. PEPTIDE SYNTHESIS

Peptides were synthesized using Fast Moc chemistry on an Applied Biosystems Model 431A peptide synthesizer. Generally, unless otherwise noted, the peptides contained amidated carboxy termini and acetylated amino termini. Amidated peptides were prepared using Rink resin (Advanced Chemtech) while peptides containing free carboxy termini were synthesized on Wang (p-alkoxy-benzyl-alcohol) resin (Bachem). First residues were double coupled to the appropriate resin and subsequent residues were single coupled. Each coupling step was followed by acetic anhydride capping. Peptides were cleaved from the resin by treatment with trifluoracetic acid (TFA) (10ml), H_2O (0.5ml), thioanisole (0.5ml), ethanedithiol (0.25ml), and crystalline phenol (0.75g). Purifi-

cation was carried out by reverse phase HPLC. Approximately 50mg samples of crude peptide were chromatographed on a Waters Delta Pak C18 column (19mm x 30cm, 15μ spherical) with a linear gradient; H_2O/acetonitrile 0.1% TFA. Lyophilized peptides were stored desiccated and peptide solutions were made in water at about 1mg/ml. Electrospray mass spectrometry yielded the following results: DP178 (SEQ ID:1):4491.87 (calculated 4491.94); DP-180 (SEQ ID:2):4491.45 (calculated 4491.94); DP-185 (SEQ ID:3):not done (calculated 4546.97).

6.1.2. VIRUS

The HIV-1_{LAI} virus was obtained from R. Gallo (Popovic, M. et al., 1984, Science 224:497-508) and propagated in CEM cells cultured in RPMI 1640 containing 10% fetal calf serum. Supernatant from the infected CEM cells was passed through a 0.2μm filter and the infectious titer estimated in a microinfectivity assay using the AA5 cell line to support virus replication. For this purpose, 25μl of serial diluted virus was added to 75μl AA5 cells at a concentration of 2 x 10^5/ml in a 96-well microtitre plate. Each virus dilution was tested in triplicate. Cells were cultured for eight days by addition of fresh medium every other day. On day 8 post infection, supernatant samples were tested for virus replication as evidenced by reverse transcriptase activity released to the supernatant. The $TCID_{50}$ was calculated according to the Reed and Muench formula (Reed, L.J. et al., 1938, Am. J. Hyg. 27:493-497). The titer of the HIV-1_{LAI} and HIV-1_{MN} stocks used for these studies, as measured on the AA5 cell line, was approximately 1.4 x 10^6 and 3.8 x 10^4 $TCID_{50}$/ml, respectively.

6.1.3. CELL FUSION ASSAY

Approximately 7 x 10^4 Molt cells were incubated with 1 x 10^4 CEM cells chronically infected with the HIV-1_{LAI} virus in 96-well plates (one-half area cluster plates; Costar, Cambridge, MA) in a final volume of 100μl culture medium as previously described (Matthews, T.J. et al., 1987, Proc. Natl. Acad. Sci. USA 84: 5424-5428). Peptide inhibitors were added in a volume of 10μl and the cell mixtures were incubated for 24 hr. at 37°C. At that time, multinucleated

giant cells were estimated by microscopic examination at a 40x magnification which allowed visualization of the entire well in a single field.

6.1.4. CELL FREE VIRUS INFECTION ASSAY

Synthetic peptides were incubated at 37°C with either 247 $TCID_{50}$ (for experiment depicted in FIG. 2), or 62 $TCID_{50}$ (for experiment depicted in FIG.3) units of HIV-1_{LAI} virus or 25 $TCID_{50}$ units of HIV-2_{NIHZ} and CEM $CD4^+$ cells at peptide concentrations of 0, 0.04, 0.4, 4.0, and 40μg/ml for 7 days. The resulting reverse transcriptase (RT) activity in counts per minute was determined using the assay described, below, in Section 6.1.5. See, Reed, L.J. et al., 1938, Am. J. Hyg. 27: 493-497 for an explanation of $TCID_{50}$ calculations.

6.1.5. REVERSE TRANSCRIPTASE ASSAY

The micro-reverse transcriptase (RT) assay was adapted from Goff et al. (Goff, S. et al., 1981, J. Virol. 38:239-248) and Willey et al. (Willey, R. et al., 1988, J. Virol. 62:139-147). Supernatants from virus/cell cultures are adjusted to 1% Triton-X100. A 10μl sample of supernatant was added to 50μl of RT cocktail in a 96-well U-bottom microtitre plate and the samples incubated at 37°C for 90 min. The RT cocktail contained 75mM KCl, 2mM dithiothreitol, 5mM $MgCl_2$, 5μg/ml poly A (Pharmacia, cat. No. 27-4110-01), 0.25 units/ml oligo dT (Pharmacia, cat. No. 27-7858-01), 0.05% NP40, 50mM Tris-HCl, pH 7.8, 0.5μM non-radioactive dTTP, and 10μCi/ml ^{32}P-dTTP (Amersham, cat. No. PB.10167).

After the incubation period, 40μl of reaction mixture was applied to a Schleicher and Schuell (S+S)

NA45 membrane (or DE81 paper) saturated in 2 x SSC buffer (0.3M NaCl and 0.003M sodium citrate) held in a S+S Minifold over one sheet of GB003 (S+S) filter paper, with partial vacuum applied. Each well of the minifold was washed four times with 200µl 2xSSC, under full vacuum. The membrane was removed from the minifold and washed 2 more times in a pyrex dish with an excess of 2xSSC. Finally, the membrane was drained on absorbent paper, placed on Whatman #3 paper, covered with Saran wrap, and exposed to film overnight at -70°C.

6.2. RESULTS

6.2.1. PEPTIDE INHIBITION OF INFECTED CELL-INDUCED SYNCYTIA FORMATION

The initial screen for antiviral activity assayed peptides' ability to block syncytium formation induced by overnight co-cultivation of uninfected Molt4 cells with chronically HIV-1 infected CEM cells. The results of several such experiments are presented herein. In the first of these experiments, serial DP178 (SEQ ID:1) peptide concentrations between 10µg/ml and 12.5ng/ml were tested for blockade of the cell fusion process. For these experiments, CEM cells chronically infected with either HIV-1_{LAI}, HIV-1_{MN}, HIV-1_{RF}, or HIV-1_{SF2} virus were cocultivated overnight with uninfected Molt 4 cells. The results (FIG. 4) show that DP178 (SEQ ID:1) afforded complete protection against each of the HIV-1 isolates down to the lowest concentration of DP178 (SEQ ID:1) used. For HIV_{LAI} inhibition, the lowest concentration tested was 12.5ng/ml; for all other HIV-1 viruses, the lowest concentration of DP178 (SEQ ID:1) used in this study was 100ng/ml. A second peptide, DP-180 (SEQ ID:2),

containing the same amino acid residues as DP178 (SEQ ID:1) but arranged in a random order exhibited no evidence of anti-fusogenic activity even at the high concentration of 40μg/ml (FIG. 4). These observations indicate that the inhibitory effect of DP178 (SEQ ID:1) is primary sequence-specific and not related to non-specific peptide/protein interactions. The actual endpoint (i.e., the lowest effective inhibitory concentration) of DP178 inhibitory action is within the range of 1-10 ng/ml.

The next series of experiments involved the preparation and testing of a DP178 (SEQ ID:1) homolog for its ability to inhibit HIV-1-induced syncytia formation. As shown in FIG. 1, the sequence of DP-185 (SEQ ID:3) is slightly different from DP178 (SEQ ID:1) in that its primary sequence is taken from the HIV-1_{SF2} isolate and contains several amino acid differences relative to DP178 (SEQ ID:1) near the N terminus. As shown in FIG. 4, DP-185 (SEQ ID:3), exhibits inhibitory activity even at 312.5ng/ml, the lowest concentration tested.

The next series of experiments involved a comparison of DP178 (SEQ ID:1) HIV-1 and HIV-2 inhibitory activity. As shown in FIG. 5, DP178 (SEQ ID:1) blocked HIV-1-mediated syncytia formation at peptide concentrations below 1ng/ml. DP178 (SEQ ID:1) failed, however, to block HIV-2 mediated syncytia formation at concentrations as high as 10μg/ml. This striking 4 log selectivity of DP178 (SEQ ID:1) as an inhibitor of HIV-1-mediated cell fusion demonstrates an unexpected HIV-1 specificity in the action of DP178 (SEQ ID:1). DP178 (SEQ ID:1) inhibition of HIV-1-mediated cell fusion, but the peptide's inability to inhibit HIV-2 medicated cell fusion in the same cell

type at the concentrations tested provides further evidence for the high degree of selectivity associated with the antiviral action of DP178 (SEQ ID:1).

6.2.2. PEPTIDE INHIBITION OF INFECTION BY CELL-FREE VIRUS

DP178 (SEQ ID:1) was next tested for its ability to block CD-4+ CEM cell infection by cell free HIV-1 virus. The results, shown in FIG. 2, are from an experiment in which DP178 (SEQ ID:1) was assayed for its ability to block infection of CEM cells by an HIV-1_{LAI} isolate. Included in the experiment were three control peptides, DP-116 (SEQ ID:9), DP-125 (SEQ ID:8), and DP-118 (SEQ ID:10). DP-116 (SEQ ID:9) represents a peptide previously shown to be inactive using this assay, and DP-125 (SEQ ID:8; Wild, C. et al., 1992, Proc. Natl. Acad, Sci. USA 89:10,537) and DP-118 (SEQ ID:10) are peptides which have previously been shown to be active in this assay. Each concentration (0, 0.04, 0.4, 4, and 40μg/ml) of peptide was incubated with 247 $TCID_{50}$ units of HIV-1_{LAI} virus and CEM cells. After 7 days of culture, cell-free supernatant was tested for the presence of RT activity as a measure of successful infection. The results, shown in FIG. 2, demonstrate that DP178 (SEQ ID:1) inhibited the de novo infection process mediated by the HIV-1 viral isolate at concentrations as low as 90ng/ml (IC50=90ng/ml). In contrast, the two positive control peptides, DP-125 (SEQ: ID:8) and DP-118 (SEQ ID:10), had over 60-fold higher IC50 concentrations of approximately 5μg/ml.

In a separate experiment, the HIV-1 and HIV-2 inhibitory action of DP178 (SEQ ID:1) was tested with CEM cells and either HIV-1_{LAI} or HIV-2_{NIH2}. 62 $TCID_{50}$

$HIV\text{-}1_{LAI}$ or 25 $GCID_{50}$ $HIV\text{-}2_{NIHZ}$ were used in these experiments, and were incubated for 7 days. As may be seen in FIG. 3, DP178 (SEQ ID:1) inhibited HIV-1 infection with an IC50 of about 31ng/ml. In contrast, DP178 (SEQ ID:1) exhibited a much higher IC50 for $HIV\text{-}2_{NIHZ}$, thus making DP178 (SEQ ID:1) two logs more potent as a HIV-1 inhibitor than a HIV-2 inhibitor. This finding is consistent with the results of the fusion inhibition assays described, above, in Section 6.2.1, and further supports a significant level of selectivity (i.e., for HIV-1 over HIV-2).

7. EXAMPLE: THE HIV-1 INHIBITOR, DP178 (SEQ ID:1) IS NON-CYTOTOXIC

In this Example, the 36 amino acid synthetic peptide inhibitor DP178 (SEQ ID:1) is shown to be non-cytotoxic to cells in culture, even at the highest peptide concentrations (40μg/ml) tested.

7.1. MATERIALS AND METHODS

Cell proliferation and toxicity assay: Approximately $3.8x10^5$ CEM cells for each peptide concentration were incubated for 3 days at 37°C in T25 flasks. Peptides tested were DP178 (SEQ ID:1) and DP-116 (SEQ ID:9), as described in FIG. 1. Peptides were synthesized as described, above, in Section 6.1. The concentrations of each peptide used were 0, 2.5, 10, and 40μg/ml. Cell counts were taken at incubation times of 0, 24, 48, and 72 hours.

7.2. RESULTS

Whether the potent HIV-1 inhibitor DP178 (SEQ ID:1) exhibited any cytotoxic effects was assessed by assaying the peptide's effects on the proliferation

and viability of cells in culture. CEM cells were incubated in the presence of varying concentrations of DP178 (SEQ ID:1), and DP-116 (SEQ ID:9), a peptide previously shown to be ineffective as a HIV inhibitor (Wild, C. et al., 1992, Proc. Natl. Acad. Sci. USA 89:10,537-10,541). Additionally, cells were incubated in the absence of either peptide.

The results of the cytotoxicity study demonstrate that DP178 (SEQ ID:1) exhibits no cytotoxic effects on cells in culture. As can be seen, below, in Table VI, even the proliferation and viability characteristics of cells cultured for 3 days in the presence of the highest concentration of DP178 (SEQ ID:1) tested (40μg/ml) do not significantly differ from the DP-116 (SEQ ID:9) or the no-peptide controls. The cell proliferation data is also represented in graphic form in FIG. 6. As was demonstrated in the Working Example presented above in Section 6, DP178 (SEQ ID:1) completely inhibits HIV-1 mediated syncytia formation at peptide concentrations between 1 and 10ng/ml, and completely inhibits cell-free viral infection at concentrations of at least 90ng/ml. Thus, this study demonstrates that even at peptide concentrations greater than 3 log higher than the HIV inhibitory dose, DP178 (SEQ ID:1) exhibits no cytotoxic effects.

Table VI

Peptide	Peptide Concentration μg/ml	% Viability at time (hours) 0	24	48	72
DP178 (SEQ ID:1)	40	98	97	95	97
	10	98	97	98	98
	2.5	98	93	96	96
DP116 (SEQ ID:9)	40	98	95	98	97
	10	98	95	93	98
	2.5	98	96	98	99
No Peptide	0	98	97	99	98

8. EXAMPLE: THE INTERACTION OF DP178 AND DP107

Soluble recombinant forms of gp41 used in the example described below provide evidence that the DP178 peptide associates with a distal site on gp41 whose interactive structure is influenced by the DP107 leucine zipper motif. A single mutation disrupting the coiled-coil structure of the leucine zipper domain transformed the soluble recombinant gp41 protein from an inactive to an active inhibitor of HIV-1 fusion. This transformation may result from liberation of the potent DP178 domain from a molecular clasp with the

leucine zipper, DP107, determinant. The results also indicate that the anti-HIV activity of various gp41 derivatives (peptides and recombinant proteins) may be due to their ability to form complexes with viral gp41 and interfere with its fusogenic process.

8.1. MATERIALS AND METHODS

8.1.1. CONSTRUCTION OF FUSION PROTEINS AND GP41 MUTANTS

Construction of fusion proteins and mutants shown in FIG. 7 was accomplished as follows: the DNA sequence corresponding to the extracellular domain of gp41 (540-686) was cloned into the Xmn I site of the expression vector pMal-p2 (New England Biolab) to give M41. The gp41 sequence was amplified from pgtat (Malim et al., 1988, Nature 355: 181-183) by using polymerase chain reaction (PCR) with upstream primer 5'-ATGACGCTGACGGTACAGGCC-3' (primer A) and downstream primer 5'-TGACTAAGCTTAATACCACAGCCAATTTGTTAT-3' (primer B). M41-P was constructed by using the T7-Gen *in vitro* mutagenesis kit from United States Biochemicals (USB) following the supplier's instructions. The mutagenic primer (5'-GGAGCTGCTTGGGGCCCCAGAC-3') introduces an Ile to Pro mutation in M41 at position 578. M41Δ107, from which the DP-107 region has been deleted, was made using a deletion mutagenic primer 5'-CCAAATCCCCAGGAGCTGCTCGAGCTGCACTATACCAGAC-3' (primer C) following the USB T7-Gen mutagenesis protocol. M41Δ178, from which the DP-178 region has been deleted, was made by cloning the DNA fragment corresponding to gp41 amino acids 540-642 into the

Xmn I site of pMal-p2. Primer A and 5'-ATAGCTTCTAGATTAATTGTTAATTTCTCTGTCCC-3' (primer D) were used in the PCR with the template pgtat to generate the inserted DNA fragments. M41-P was used as the template with primer A and D in PCR to generate M41-PΔ178. All inserted sequences and mutated residues were checked by restriction enzyme analysis and confirmed by DNA sequencing.

8.1.2. PURIFICATION AND CHARACTERIZATION OF FUSION PROTEINS

The fusion proteins were purified according to the protocol described in the manufacturer's brochure of protein fusion and purification systems from New England Biolabs (NEB). Fusion proteins (10 ng) were analyzed by electrophoresis on 8% SDS polyacrylamide gels. Western blotting analysis was performed as described by Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2d Ed, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, Ch. 18, pp. 64-75. An HIV-1 positive serum diluted 1000-fold, or a human Fab derived from repertoire cloning was used to react with the fusion proteins. The second antibody was HRP-conjugated goat antihuman Fab. An ECL Western blotting detection system (Amersham) was used to detect the bound antibody. A detailed protocol for this detection system was provided by the manufacturer. Rainbow molecular weight markers (Amersham) were used to estimate the size of fusion proteins.

8.1.3. CELL FUSION ASSAYS FOR ANTI-HIV ACTIVITY

Cell fusion assays were performed as previously described (Matthews et al., 1987, Proc. Natl. Acad.

Sci. USA 84: 5424-5481). CEM cells (7 X 10^4) were incubated with HIV-1_{IIIB} chronically infected CEM cells (10^4) in 96-well flat-bottomed half-area plates (Costar) in 100 μl culture medium. Peptide and fusion proteins at various concentrations in 10 μl culture medium were incubated with the cell mixtures at 37°C for 24 hours. Multinucleated syncytia were estimated with microscopic examination. Both M41 and M41-P did not show cytotoxicity at the concentrations tested and shown in FIG. 8.

Inhibition of HIV-1 induced cell-cell fusion activity was carried out in the presence of 10 nM DP178 and various concentrations of M41Δ178 or M41-PΔ178 as indicated in FIG. 9. There was no observable syncytia in the presence of 10 nM DP178. No peptide or fusion protein was added in the control samples.

8.1.4. ELISA ANALYSIS OF DP178 BINDING TO THE LEUCINE ZIPPER MOTIF OF GP41

The amino acid sequence of DP178 used is: YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF. For enzyme linked immunoassay (ELISA), M41Δ178 or M41-PΔ178 (5 μg/ml) in 0.1M $NaHCO_3$, pH 8.6, were coated on 96 wells Linbro ELISA plates (Flow Lab, Inc.) overnight. Each well was washed three times with distilled water then blocked with 3% bovine serum albumin (BSA) for 2 hours. After blocking, peptides with 0.5% BSA in TBST (40 mM Tris-HCl pH7.5, 150 mM NaCl, 0.05% Tween 20) were added to the ELISA plates and incubated at room temperature for 1 hour. After washing three times with TBST, Fab-d was added at a concentration of 10 ng/ml with 0.5% BSA in TBST. The plates were washed three times with TBST after incubation at room temperature for 1 hour. Horse radish peroxidase (HRP)

conjugated goat antihuman Fab antiserum at a 2000 fold dilution in TBST with 0.5% BSA was added to each well and incubated at room temperature for 45 minutes. The plates were then washed four times with TBST. The peroxidase substrate o-phenylene diamine (2.5 mg/ml) and 0.15% H_2O_2 were added to develop the color. The reaction was stopped with an equal volume of 4.5 N H_2SO_4 after incubation at room temperature for 10 minutes. The optical density of the stopped reaction mixture was measured with a micro plate reader (Molecular Design) at 490 nm. Results are shown in FIG. 10.

8.2. RESULTS

8.2.1. THE EXPRESSION AND CHARACTERIZATION OF THE ECTODOMAIN OF gp41

As a step toward understanding the roles of the two helical regions in gp41 structure and function, the ectodomain of gp41 was expressed as a maltose binding fusion protein (M41) (FIG. 7). The fusogenic peptide sequence at the N-terminal of gp41 was omitted from this recombinant protein and its derivatives to improve solubility. The maltose binding protein facilitated purification of the fusion proteins under relatively mild, non-denaturing conditions. Because the M41 soluble recombinant gp41 was not glycosylated, lacked several regions of the transmembrane protein (i.e., the fusion peptide, the membrane spanning, and the cytoplasmic domains), and was expressed in the absence of gp120, it was not expected to precisely reflect the structure of native gp41 on HIV-1 virions. Nevertheless, purified M41 folded in a manner that preserved certain discontinuous epitopes as evidenced by reactivity with human monoclonal antibodies, 98-6,

126-6, and 50-69, previously shown to bind conformational epitopes on native gp41 expressed in eukaryotic cells (Xu et al., 1991, J. Virol. 65: 4832-4838; Chen, 1994, J. Virol. 68:2002-2010). Thus, at least certain regions of native gp41 defined by these antibodies appear to be reproduced in the recombinant fusion protein M41. Furthermore, M41 reacted with a human recombinant Fab (Fab-d) that recognizes a conformational epitope on gp41 and binds HIV-1 virions as well as HIV-1 infected cells but not uninfected cells as analyzed by FACS. Deletion of either helix motif, i.e., DP107 or DP178, of the M41 fusion protein eliminated reactivity with Fab-d. These results indicate that both helical regions, separated by 60 amino acids in the primary sequence, are required to maintain the Fab-d epitope.

8.2.2. ANTI-HIV ACTIVITY OF THE RECOMBINANT ECTODOMAIN OF GP41

The wild type M41 fusion protein was tested for anti-HIV-1 activity. As explained, supra, synthetic peptides corresponding to the leucine zipper (DP107) and the C-terminal putative helix (DP178) show potent anti-HIV activity. Despite inclusion of both these regions, the recombinant M41 protein did not affect HIV-1 induced membrane fusion at concentrations as high as 50 μM (Table VII, below).

Table VII

DISRUPTION OF THE LEUCINE ZIPPER OF GP41 FREES THE ANTI-HIV MOTIF

	DP107	DP178	M41	M41-P	M41-PΔ178
Cell fusion (IC_{90})	1 μM	1 nM	>50 μM	83 nM	>50 μM
Fab-D binding (k_D)	-	-	$3.5x10^{-9}$	$2.5x10^{-8}$	-
HIV infectivity (IC_{90})	1 μM	80 nM	>16 μM	66 nM	>8 μM

1 The affinity constants of Fab-d binding to the fusion proteins were determined using a protocol described by B. Friguet et al., 1985, J. Immunol. Method. 77:305-319.

- = No detectable binding of Fab-d to the fusion proteins.

Antiviral Infectivity Assays. 20 μl of serially diluted virus stock was incubated for 60 minutes at ambient temperature with 20 μl of the indicated concentration of purified recombinant fusion protein in RPMI 1640 containing 10% fetal bovine serum and antibiotics in a 96-well microtiter plate. 20 μl of CEM4 cells at 6 x 10^5 cells/ml were added to each well, and cultures were incubated at 37°C in a humidified CO_2 incubator. Cells were cultured for 9 days by the addition of fresh medium every 2 to 3 days. On days 5, 7, and 9 postinfection, supernatant samples were assayed for reverse transcriptase (RT) activity, as described below, to monitor viral replication. The 50% tissue culture infectious dose ($TCID_{50}$) was calculated for each condition according to the formula of Reed & Muench, 1937, Am. J. Hyg. 27:493-497. RT activity was determined by a modification of the published methods of Goff et al., 1981, J. Virol. 38:239-248 and Willey et al., 1988, J. Virol. 62:139-147 as described in Chen et al., 1993, AIDS Res. Human Retroviruses 9:1079-1086.

Surprisingly, a single amino acid substitution, proline in place of isoleucine in the middle of the leucine zipper motif, yielded a fusion protein (M41-P) which did exhibit antiviral activity (Table XXV and Fig. 8). As seen in Table XXV, M41-P blocked syncytia

formation by 90% at approximately 85 nM and neutralized HIV-1_{IIIB} infection by 90% at approximately 70 nM concentrations. The anti-HIV-1 activity of M41-P appeared to be mediated by the C-terminal helical sequence since deletion of that region from M41-P yielded an inactive fusion protein, M41-PΔ178 (Table XXV). This interpretation was reinforced by experiments demonstrating that a truncated fusion protein lacking the DP178 sequence, M41Δ178, abrogated the potent anti-fusion activity of the DP178 peptide in a concentration-dependent manner (FIG. 9). The same truncated fusion protein containing the proline mutation disrupting the leucine zipper, M41-PΔ178, was not active in similar competition experiments (FIG. 9). The results indicate that the DP178 peptide associates with a second site on gp41 whose interactive structure is dependent on a wild type leucine zipper sequence. A similar interaction may occur within the wild type fusion protein, M41, and act to form an intramolecular clasp which sequesters the DP178 region, making it unavailable for anti-viral activity.

A specific association between these two domains is also indicated by other human monoclonal Fab-d studies. For example, Fab-d failed to bind either the DP178 peptide or the fusion protein M41Δ178, but its epitope was reconstituted by simply mixing these two reagents together (FIG. 10). Again, the proline mutation in the leucine zipper domain of the fusion protein, M41-PΔ178, failed to reconstitute the epitope in similar mixing experiments.

9. EXAMPLE: METHOD FOR COMPUTER-ASSISTED IDENTIFICATION OF DP107-LIKE AND DP178-LIKE SEQUENCES

A number of known coiled-coil sequences have been well described in the literature and contain heptad repeat positioning for each amino acid. Coiled-coil nomenclature labels each of seven amino acids of a heptad repeat A through G, with amino acids A and D tending to be hydrophobic positions. Amino acids E and G tend to be charged. These four positions (A, D, E, and G) form the amphipathic backbone structure of a monomeric alpha-helix. The backbones of two or more amphipathic helices interact with each other to form di-, tri-, tetrameric, etc., coiled-coil structures. In order to begin to design computer search motifs, a series of well characterized coiled coils were chosen including yeast transcription factor GCN4, Influenza Virus hemagglutinin loop 36, and human proto-oncogenes c-Myc, c-Fos, and c-Jun. For each peptide sequence, a strict homology for the A and D positions, and a list of the amino acids which could be excluded for the B, C, E, F, and G positions (because they are not observed in these positions) was determined. Motifs were tailored to the DP107 and DP178 sequences by deducing the most likely possibilities for heptad positioning of the amino acids of HIV-1 Bru DP-107, which is known to have coiled-coil structure, and HIV-1 Bru DP178, which is still structurally undefined. The analysis of each of the sequences is contained in FIG. 12. For example, the motif for GCN4 was designed as follows:

1. The only amino acids (using standard single letter amino acid codes) found in the A or D positions of GCN4 were [LMNV].

2. All amino acids were found at B, C, E, F, and G positions except {CFGIMPTW}.

3. The PESEARCH motif would, therefore, be written as follows:

[LMNV]-{CFGIMPTW}(2)-[LMNV]-{CFGIMPTW}(3)-
[LMNV]-{CFGIMPTW}(2)-[LMNV]-{CFGIMPTW}(3)-
[LMNV]-{CFGIMPTW}(2)-[LMNV]-{CFGIMPTW}(3)-
[LMNV]-{CFGIMPTW}(2)-[LMNV]-{CFGIMPTW}(3)

Translating or reading the motif: "at the first A position either L, M, N, or V must occur; at positions B and C (the next two positions) accept everything except C, F, G, I, M, P, T, or W; at the D position either L, M, N, or V must occur; at positions E, F, and G (the next 3 positions) accept everything except C, F, G, I, M, P, T, or W." This statement is contained four times in a 28-mer motif and five times in a 35-mer motif. The basic motif key then would be: [LMNV]-{CFGIMPTW}. The motif keys for the remaining well described coiled-coil sequences are summarized in FIG. 12.

The motif design for DP107 and DP178 was slightly different than the 28-mer model sequences described above due to the fact that heptad repeat positions are not defined and the peptides are both longer than 28 residues. FIG. 13 illustrates several possible sequence alignments for both DP107 and DP178 and also includes motif designs based on 28-mer, 35-mer, and full-length peptides. Notice that only slight differences occur in the motifs as the peptides are lengthened. Generally, lengthening the base peptide results in a less stringent motif. This is very useful in broadening the possibilities for identifying

DP107-or DP-178-like primary amino acid sequences referred to in this document as "hits".

In addition to making highly specific motifs for each type peptide sequence to be searched, it is also possible to make "hybrid" motifs. These motifs are made by "crossing" two or more very stringent motifs to make a new search algorithm which will find not only both "parent" motif sequences but also any peptide sequences which have similarities to one, the other, or both "parents". For example, in FIG. 14 the "parent" sequence of GCN4 is crossed with each of the possible "parent" motifs of DP-107. Now the hybrid motif must contain all of the amino acids found in the A and D positions of both parents, and exclude all of the amino acids not found in either parent at the other positions. The resulting hybrid from crossing GCN4 or [LMNV]{CFGIMPTW} and DP107 (28-mer with the first L in the D position) or [ILQT]{CDFIMPST}, is [ILMNQTV]{CFIMPT}. Notice that now only two basic hybrid motifs exist which cover both framing possibilities, as well as all peptide lengths of the parent DP-107 molecule. FIG. 15 represents the "hybridizations" of GCN4 with DP-178. FIG. 16 represents the "hybridizations" of DP107 and DP178. It is important to keep in mind that the represented motifs, both parent and hybrid, are motif keys and not the depiction of the full-length motif needed to actually do the computer search.

Hybridizations can be performed on any combination of two or more motifs. FIG. 17 summarizes several three-motif hybridizations including GCN4, DP107 (both frames), and DP178 (also both frames). Notice that the resulting motifs are now becoming much more similar to each other. In

fact, the first and third hybrid motifs are actually subsets of the second and fourth hybrid motifs respectively. This means that the first and third hybrid motifs are slightly more stringent than the second and fourth. It should also be noted that with only minor changes in these four motifs, or by hybridizing them, a single motif could be obtained which would find all of the sequences. However, it should be remembered that stringency is also reduced. Finally, the most broad-spectrum and least-stringent hybrid motif is described in FIG. 18 which summarizes the hybridization of GCN4, DP107 (both frames), DP178 (both frames), c-Fos, c-Jun, c-Myc, and Flu loop 36.

A special set of motifs was designed based on the fact that DP-178 is located only approximately ten amino acids upstream of the transmembrane spanning region of gp41 and just C-terminal to a proline which separates DP107 and DP178. It has been postulated that DP178 may be an amphipathic helix when membrane associated, and that the proline might aid in the initiation of the helix formation. The same arrangement was observed in Respiratory Syncytial Virus; however, the DP178-like region in this virus also had a leucine zipper just C-terminal to the proline. Therefore, N-terminal proline-leucine zipper motifs were designed to analyze whether any other viruses might contain this same pattern. The motifs are summarized in FIG. 19.

The PC/Gene protein database contains 5879 viral amino acid sequences (library file PVIRUSES; CD-ROM release 11.0). Of these, 1092 are viral enveloped or glycoprotein sequences (library file PVIRUSE1). Tables V through XIV contain lists of protein sequence

names and motif hit locations for all the motifs searched.

10. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP107 AND DP178-LIKE SEQUENCES IN HUMAN IMMUNODEFICIENCY VIRUS

FIG. 20 represents search results for HIV-1 BRU isolate gp41 (PC/Gene protein sequence PENV_HV1BR). Notice that the hybrid motif which crosses DP-107 and DP-178 (named 107x178x4; the same motif as found in FIG. 16 found three hits including amino acids 550-599, 636-688, and 796-823. These areas include DP-107 plus eight N-terminal and four C-terminal amino acids; DP178 plus seven N-terminal and ten C-terminal amino acids; and an area inside the transmembrane region (cytoplasmic). FIG. 20 also contains the results obtained from searching with the motif named ALLMOTI5, for which the key is found in FIG. 17 ({CDGHP}{CFP}x5). This motif also found three hits including DP107 (amino acids 510-599), DP178 (615-717), and a cytoplasmic region (772-841). These hits overlap the hits found by the motif 107x178x4 with considerable additional sequences on both the amino and carboxy termini. This is not surprising in that 107x178x4 is a subset of the ALLMOTI5 hybrid motif. Importantly, even though the stringency of ALLMOTI5 is considerably less than 107x178x4, it still selectively identifies the DP107 and DP178 regions of gp41 shown to contain sequences for inhibitory peptides of HIV-1. The results of these two motif searches are summarized in Table V of U.S. Patent Application Serial No. 08/470,896 filed on June 6, 1995 (incorporated herein by reference in its entirety) under the PC/Gene protein sequence name PENV_HV1BR. The proline-leucine

zipper motifs also gave several hits in HIV-1 BRU including 503-525 which is at the very C-terminus of gp120, just upstream of the cleavage site (P7LZIPC and P12LZIPC); and 735-768 in the cytoplasmic domain of gp41 (P23LZIPC). These results are found in Tables VIII, IX, and X under the same sequence name as mentioned above. Notice that the only area of HIV-1 BRU which is predicted by the Lupas algorithm to contain a coiled-coil region, is from amino acids 635-670. This begins eight amino acids N-terminal to the start and ends eight amino acids N-terminal to the end of DP178. DP107, despite the fact that it is a known coiled coil, is not predicted to contain a coiled-coil region using the Lupas method.

11. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP107-LIKE AND DP178-LIKE SEQUENCES IN HUMAN RESPIRATORY SYNCYTIAL VIRUS

FIG. 21 represents search results for Human Respiratory Syncytial Virus (RSV; Strain A2) fusion glycoprotein F1 (PC/Gene protein sequence name PVGLF_HRSVA). Motif 107x178x4 finds three hits including amino acids 152-202, 213-243, and 488-515. The arrangement of these hits is similar to what is found in HIV-1 except that the motif finds two regions with similarities to DP-178, one just downstream of what would be called the DP107 region or amino acids 213-243, and one just upstream of the transmembrane region (also similar to DP178) or amino acids 488-515. Motif ALLMOTI5 also finds three areas including amino acids 116-202, 267-302, and 506-549. The proline-leucine zipper motifs also gave several hits including amino acids 205-221 and 265-287 (P1LZIPC 265-280, P12LZIPC),

and 484-513 (P7LZIPC and P12LZIPC 484-506, P23LZIPC). Notice that the PLZIP motifs also identify regions which share location similarities with DP-178 of HIV-1.

12. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP107-LIKE AND DP178-LIKE SEQUENCES IN SIMIAN IMMUNODEFICIENCY VIRUS

Motif hits for Simian immunodeficiency Virus gp41 (AGM3 isolate; PC/Gene protein sequence name PENV_SIVAG) are shown in FIG. 22. Motif 107x178x4 finds three hits including amino acids 566-593, 597-624, and 703-730. The first two hits only have three amino acids between them and could probably be combined into one hit from 566-624 which would represent a DP107-like hit. Amino acids 703 to 730 would then represent a DP178-like hit. ALLMOTI5 also finds three hits including amino acids 556-628 (DP107-like), 651-699 (DP178-like), and 808-852 which represents the transmembrane spanning region. SIV also has one region from 655-692 with a high propensity to form a coiled coil as predicted by the Lupas algorithm. Both 107x178x4 and ALLMOTI5 motifs find the same region. SIV does not have any PLZIP motif hits in gp41.

The identification of DP178/DP107 analogs for a second SIV isolate (MM251) is demonstrated in the Example presented, below, in Section 19.

13. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP107-LIKE AND DP178 LIKE SEQUENCES IN CANINE DISTEMPER VIRUS

Canine Distemper Virus (strain Onderstepoort) fusion glycoprotein F1 (PC/Gene Protein sequence name

PVGLF_CDVO) has regions similar to Human RSV which are predicted to be DP107-like and DP178-like (FIG. 23). Motif 107x178x4 highlights one area just C-terminal to the fusion peptide at amino acids 252-293. Amino acids 252-286 are also predicted to be coiled coil using the Lupas algorithm. Almost 100 amino acids C-terminal to the first region is a DP178-like area at residues 340-367. ALLMOTI5 highlights three areas of interest including: amino acids 228-297, which completely overlaps both the Lupas prediction and the DP107-like 107x178x4 hit; residues 340-381, which overlaps the second 107x178x4 hit; and amino acids 568-602, which is DP178-like in that it is located just N-terminal to the transmembrane region. It also overlaps another region (residues 570-602) predicted by the Lupas method to have a high propensity to form a coiled coil. Several PLZIP motifs successfully identified areas of interest including P6 and P12LZIPC which highlight residues 336-357 and 336-361 respectively; P1 and P12LZIPC which find residues 398-414; and P12 and P23LZIPC which find residues 562-589 and 562-592 respectively.

14. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP107-LIKE AND DP178-LIKE SEQUENCES IN NEWCASTLE DISEASE VIRUS

FIG. 24 shows the motif hits found in Newcastle Disease Virus (strain Australia-Victoria/32; PC Gene protein sequence name PVGLF_NDVA). Motif 107x178x4 finds two areas including a DP107-like hit at amino acids 151-178 and a DP178-like hit at residues 426-512. ALLMOTI5 finds three areas including residues 117-182, 231-272, and 426-512. The hits from 426-512 include a region which is predicted by the Lupas

method to have a high coiled-coil propensity (460-503). The PLZIP motifs identify only one region of interest at amino acids 273-289 (P1 and 12LZIPC).

15. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP107-LIKE AND DP178-LIKE SEQUENCES IN HUMAN PARAINFLUENZA VIRUS

Both motifs 107x178x4 and ALLMOTI5 exhibit DP107-like hits in the same region, 115-182 and 117-182 respectively, of Human Parainfluenza Virus (strain NIH 47885; PC/Gene protein sequence name PVGLF_p13H4; (FIG. 25). In addition, the two motifs have a DP178-like hit just slightly C-terminal at amino acids 207-241. Both motifs also have DP178-like hits nearer the transmembrane region including amino acids 457-497 and 462-512 respectively. Several PLZIP motif hits are also observed including 283-303 (P5LZIPC), 283-310 (P12LZIPC), 453-474 (P6LZIPC), and 453-481 (P23LZIPC). The Lupas algorithm predicts that amino acids 122-176 may have a propensity to form a coiled-coil.

16. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP107-LIKE AND DP178-LIKE SEQUENCES OF INFLUENZA A VIRUS

FIG. 26 illustrates the Lupas prediction for a coiled coil in Influenza A Virus (strain A/Aichi/2/68) at residues 379-436, as well as the motif hits for 107x178x4 at amino acids 387-453, and for ALLMOTI5 at residues 380-456. Residues 383-471 (38-125 of HA2) were shown by Carr and Kim to be an extended coiled coil when under acidic pH (Carr and Kim, 1993, Cell 73: 823-832). The Lupas algorithm predicts a coiled-coil at residues 379-436. All three methods successfully predicted the region shown to actually

have coiled-coil structure; however, ALLMOTI5 predicted the greatest portion of the 88 residue stretch.

17. EXAMPLE: POTENTIAL RESPIRATORY SYNCYTIAL VIRUS DP178/DP107 ANALOGS: CD AND ANTIVIRAL CHARACTERIZATION

In the Example presented herein, respiratory syncytial virus (RSV) peptides identified by utilizing the computer-assisted search motifs described in the Examples presented in Sections 9 and 11, above, were tested for anti-RSV activity. Additionally, circular dichroism (CD) structural analyses were conducted on the peptides, as discussed below. It is demonstrated that several of the identified peptides exhibit potent antiviral capability. Additionally, it is shown that several of these peptides exhibit a substantial helical character.

17.1 MATERIALS AND METHODS

Structural analyses: The CD spectra were measured in a 10mM sodium phosphate, 150mM sodium chloride, pH 7.0, buffer at approximately 10mM concentrations, using a 1 cm pathlength cell on a Jobin/Yvon Autodichrograph Mark V CD spectrophotometer. Peptides were synthesized according to the methods described, above, in Section 6.1. Peptide concentrations were determined from A_{280} using Edlehoch's method (1967, Biochemistry 6:1948).

Anti-RSV antiviral activity assays: The assay utilized herein tested the ability of the peptides to disrupt the ability of HEp2 cells acutely infected with RSV (i.e., cells which are infected with a multiplicity of infection of greater than 2) to fuse

and cause syncytial formation on a monolayer of uninfected an uninfected line of Hep-2 cells. The lower the observed level of fusion, the greater the antiviral activity of the peptide was determined to be.

Uninfected confluent monolayers of Hep-2 cells were grown in microtiter wells in 3% EMEM (Eagle Minimum Essential Medium w/o L-glutamine [Bio Whittaker Cat. No. 12-125F], with fetal bovine serum [FBS; which had been heat inactivated for 30 minutes at 56°C; Bio Whittaker Cat. No. 14-501F) supplemented at 3%, antibiotics (penicillin/streptomycin; Bio Whittaker Cat. No. 17-602E) added at 1%, and glutamine added at 1%.

To prepare Hep2 cells for addition to uninfected cells, cultures of acutely infected Hep2 cells were washed with DPBS (Dulbecco's Phosphate Buffered Saline w/o calcium or magnesium; Bio Whittaker Cat. No. 17-512F) and cell monolayers were removed with Versene (1:5000; Gibco Life Technologies Cat. No. 15040-017). The cells were spun 10 minutes and resuspended in 3% FBS. Cell counts were performed using a hemacytometer. Persistent cells were added to the uninfected Hep-2 cells.

The antiviral assay was conducted by, first, removing all media from the wells containing uninfected Hep-2 cells, then adding peptides (at the dilutions described below) in 3% EMEM, and 100 acutely RSV-infected Hep2 cells per well. Wells were then incubated at 37°C for 48 hours.

After incubation, cells in control wells were checked for fusion centers, media was removed from the wells, followed by addition, to each well, of either Crystal Violet stain or XTT. With respect to Crystal

Violet, approximately 50μl 0.25% Crystal Violet stain in methanol were added to each well. The wells were rinsed immediately, to remove excess stain, and were allowed to dry. The number of syncytia per well were then counted, using a dissecting microscope.

With respect to XTT (2,3-bis[2-Methoxy-4-nitro-5-sulfophenyl]-2H-tetrazolium-5-carboxyanilide inner salt), 50μl XTT (1mg/ml in RPMI buffered with 100mM HEPES, pH 7.2-7.4, plus 5% DMSO) were added to each well. The $OD_{450/690}$ was measured (after blanking against growth medium without cells or reagents, and against reagents) according to standard procedures.

Peptides: The peptides characterized in the study presented herein were:

1) peptides T-142 to T-155 and T-575, as shown in FIG. 27A, and peptides T-22 to T-27, T-68, T-334 and T-371 to T-375 and T-575, as shown in FIG. 27B;

2) peptides T-120 to T-141 and T-576, as shown in FIG. 27B, and peptides T-12, T-13, T-15, T-19, T-28 to T-30, T-66, T-69, T-70 and T-576, as shown in FIG. 27D; and

3) peptides T-67 and T-104 to T-119 and T-384, as shown in FIG. 28A, and peptides T-71, T-613 to T-617, T-662 to T-676 and T-730, as shown in FIG. 28B.

The peptides of group 1 represent portions of the RSV F2 protein DP178/107-like region. The peptides of group 2 represent portions of the RSV F1 protein DP107-like region. The peptides of groups 3 represent portions of the RSV F1 protein DP178-like region.

Each peptide was tested at 2-fold serial dilutions ranging from 100μg/ml to approximately 100ng/ml. For each of the assays, a well containing no peptide was also used. The IC_{50} data for each

peptide represents the average of several experiments conducted utilizing that peptide.

17.2 RESULTS

The data summarized in FIGS. 27A-B and 28A-B represent antiviral and structural information obtained from peptides derived from the RSV F2 DP178/DP107-like F2 region (FIG. 27A-B), the RSV F1 DP-107-like region (FIG. 27C-D) and the RSV DP178-like F2 region (FIG. 28A-B).

As shown in FIGS. 27A-D, a number of the RSV DP178/DP107-like peptides exhibited a detectable level of antiviral activity. Peptides from the RSV DP178/DP107-like F2 region (FIG. 27A-B), for example, T-142 to T-145 and T-334 purfied peptides, exhibited detectable levels of antiviral activity, as evidenced by their IC_{50} values. Further, a number of RSV F1 DP107-like peptides (FIG. 27C-D) exhibited a sizable level of antiviral activity as purified peptides, including, for example, peptides T-124 to T-127, T-131, T-135 and T-137 to T-139, as demonstrated by their low IC_{50} values. In addition, CD analysis FIG. 27A, 27C) reveals that many of the peptides exhibit some detectable level of helical structure.

The results summarized in FIG. 28A-B demonstrate that a number of DP178-like purified peptides exhibit a range of potent anti-viral activity. These peptides include, for example, T-67, T-104, T-105 and T-107 to T-119, as listed in FIG. 28A, and T-665 to T-669 and T-671 to T-673, as listed in FIG. 28B. In addition, some of the DP178-like peptides exhibited some level of helicity.

Thus, the computer assisted searches described, hereinabove, successfully identified viral peptide

domains that represent highly promising anti-RSV antiviral compounds.

18. EXAMPLE: POTENTIAL HUMAN PARAINFLUENZA VIRUS TYPE 3 DP178/DP107 ANALOGS: CD AND ANTIVIRAL CHARACTERIZATION

In the Example presented herein, human parainfluenza virus type 3 (HPIV3) peptides identified by utilizing the computer-assisted search motifs described in the Examples presented in Sections 9 and 15, above, were tested for anti-HPIV3 activity. Additionally, circular dichroism (CD) structural analyses were conducted on the peptides, as discussed below. It is demonstrated that several of the identified peptides exhibit potent antiviral capability. Additionally, it is shown that several of these peptides exhibit a substantial helical character.

18.1 MATERIALS AND METHODS

Structural analyses: Structural analyses consisted of circular dichroism (CD) studies. The CD spectra were measured in a 10mM sodium phosphate, 150mM sodium chloride, pH 7.0, buffer at approximately 10mM concentrations, using a 1 cm pathlength cell on a Jobin/Yvon Autodichrograph Mark V CD spectrophotometer. Peptide concentrations were determined from A_{280} using Edlehoch's method (1967, Biochemistry 6:1948).

Anti-HPIV3 antiviral activity assays: The assay utilized herein tested the ability of the peptides to disrupt the ability of Hep2 cells chronically infected with HPIV3 to fuse and cause syncytial formation on a monolayer of an uninfected line of CV-1W cells. The

more potent the lower the observed level of fusion, the greater the antiviral activity of the peptide.

Uninfected confluent monolayers of CV-1W cells were grown in microtiter wells in 3% EMEM (Eagle Minimum Essential Medium w/o L-glutamine [Bio Whittaker Cat. No. 12-125F], with fetal bovine serum [FBS; which had been heat inactivated for 30 minutes at 56°C; Bio Whittaker Cat. No. 14-501F) supplemented at 3%, antibiotics/antimycotics (Gibco BRL Life Technologies Cat. No. 15040-017) added at 1%, and glutamine added at 1%.

To prepare Hep2 cells for addition to uninfected cells, cultures of chronically infected Hep2 cells were washed with DPBS (Dulbecco's Phosphate Buffered Saline w/o calcium or magnesium; Bio Whittaker Cat. No. 17-512F) and cell monolayers were removed with Versene (1:5000; Gibco Life Technologies Cat. No. 15040-017). The cells were spun 10 minutes and resuspended in 3% FBS. Cell counts were performed using a hemacytometer. Persistent cells were added to the uninfected CV-1W cells.

The antiviral assay was conducted by, first, removing all media from the wells containing uninfected CV-1W cells, then adding peptides (at the dilutions described below) in 3% EMEM, and 500 chronically HPIV3-infected Hep2 cells per well. Wells were then incubated at 37°C for 24 hours.

On day 2, after cells in control wells were checked for fusion centers, media was removed from the wells, followed by addition, to each well, of approximately 50μl 0.25% Crystal Violet stain in methanol. Wells were rinsed immediately, to remove excess stain and were then allowed to dry. The number

of syncytia per well were then counted, using a dissecting microscope.

Alternatively, instead of Crystal Violet analysis, cells were assayed with XTT, as described, avove, in Section 17.1.

Peptides: The peptides characterized in the study presented herein were:

1) Peptides 157 to 188, as shown in FIG. 29A, and peptides T-38 to T-40, T-42 to T-46 and T-582, as shown in FIG. 29B. These peptides are derived from the DP107 region of the HPIV3 F1 fusion protein (represented by HPF3 107, as shown in FIG. 29A); and

2) Peptides 189 to 210, as shown in FIG. 30A, and T-269, T-626, T-383 and T-577 to T-579, as shown in FIG. 30B. These peptides are primarily derived from the DP178 region of the HPIV3 F1 fusion protein (represented by HPF3 178, as shown in FIG. 30A). Peptide T-626 contains two mutated amino acid resides (represented by a shaded background). Additionally, peptide T-577 represents F1 amino acids 65-100, T-578 represents F1 amino acids 207-242 and T-579 represents F1 amino acids 273-309.

Each peptide was tested at 2-fold serial dilutions ranging from 500μg/ml to approximately 500ng/ml. For each of the assays, a well containing no peptide was also used.

18.2 RESULTS

The data summarized in FIGS. 29A-C and 30A-B represent antiviral and structural information obtained from peptides derived from the HPIV3 fusion

protein DP107-like region (FIG. 29A-C) and the HPIV3 fusion protein DP178-like region (FIG. 30A-B).

As shown in FIG. 29A-B, a number of the HPIV3 DP107-like peptides exhibited potent levels of antiviral activity. These peptides include, for example, peptides T-40, T-172 to T-175, T-178, T-184 and T-185.

CD analysis reveals that a number of the peptides exhibit detectable to substantial level of helical structure. The CD spectra for one of the peptides, 184, which exhibits substantial helicity is summarized in FIG. 29C.

The results summarized in FIG. 30A-B demonstrate that a number of the DP178-like peptides tested exhibit a range of anti-viral activity. These peptides include, for example, peptides 194 to 211, as evidenced by their low IC_{50} values. In fact, peptides 201 to 205 exhibit IC_{50} values in the nanogram/ml range. In addition, many of the DP178-like peptides exhibited some level of helicity.

Thus, the computer assisted searches described, hereinabove, have successfully identified viral peptide domains that represent highly promising anti-HPIV3 antiviral compounds.

19. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP178/DP107 ANALOGS IN SIMIAN IMMUNODEFICIENCY VIRUS

FIG. 31 represents search results for SIV isolate MM251 (PC/Gene® protein sequence PENV_SIVM2). Both 107x178x4 and ALLMOTI5 search motifs identified two regions with similarities to DP107 and/or DP178.

The peptide regions found by 107x178x4 were located at amino acid residues 156-215 and 277-289.

The peptide regions found by ALLMOTI5 were located at amino acid residues 156-219 and 245-286. Both motifs, therefore, identify similar regions.

Interestingly, the first SIV peptide region (i.e., from amino acid residue 156 to approximately amino acid residue 219) correlates with a DP107 region, while the second region identified (i.e., from approximately amino acid residue 245 to approximately amino acid residue 289) correlates with the DP178 region of HIV. In fact, an alignment of SIV isolate MM251 and HIV isolate BRU, followed by a selection of the best peptide matches for HIV DP107 and DP178, reveals that the best matches are found within the peptide regions identified by the 107x178x4 and ALLMOTI5 search motifs.

It should be noted that a potential coiled-coil region at amino acid residues 242-282 is predicted by the Lupas program. This is similar to the observation in HIV in which the coiled-coil is predicted by the Lupas program to be in the DP178 rather than in the DP107 region. It is possible, therefore, that SIV may be similar to HIV in that it may contain a coiled-coil structure in the DP107 region, despite such a structure being missed by the Lupas algorithm. Likewise, it may be that the region corresponding to a DP178 analog in SIV may exhibit an undefined structure, despite the Lupas program's prediction of a coiled-coil structure.

20. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP178/DP107 ANALOGS IN EPSTEIN-BARR VIRUS

The results presented herein describe the identification of DP178/DP107 analogs within two

different Epstein-Barr Virus proteins. Epstein-Barr is a human herpes virus which is the causative agent of, for example, infectious mononucleosis (IM), and is also associated with nasopharyngeal carcinomas (NPC), Burkitt's lymphoma and other diseases. The virus predominantly exists in the latent form and is activated by a variety of stimuli.

FIG. 32 depicts the search motif results for the Epstein-Barr Virus (Strain B95-8; PC/Gene® protein sequence PVGLB_EBV) glycoprotein gp110 precursor (gp115). The 107x178x4 motif identified two regions of interest, namely the regions covered by amino acid residues 95-122 and 631-658. One PZIP region was identified at amino acid residue 732-752 which is most likely a cytoplasmic region of the protein. The Lupas algorithm predicts a coiled-coil structure for amino acids 657-684. No ALLMOTIS regions were identified.

FIG. 33 depicts the search motif results for the Zebra (or EB1) trans-activator protein (BZLF1) of the above-identified Epstein-Barr virus. This protein is a transcription factor which represents the primary mediator of viral reactivation. It is a member of the b-ZIP family of transcription factors and shares significant homology with the basic DNA-binding and dimerization domains of the cellular oncogenes c-fos and C/EBP. The Zebra protein functions as a homodimer.

Search results domonstrate that the Zebra protein exhibits a single region which is predicted to be either of DP107 or DP178 similarity, and is found between the known DNA binding and dimerization regions of the protein. Specifically, this region is located at amino acid residues 193-220, as shown in FIG. 33. The Lupas program predicted no coiled-coil regions.

21. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP178/DP107 ANALOGS IN MEASLES VIRUS

FIG. 34 illustrates the motif search results for the fusion protein F1 of measles virus, strain Edmonston (PC Gene® protein sequence PVGLF_MEASE), successfully identifying DP178/DP107 analogs.

The 107x178x4 motif identifies a single region at amino acid residues 228-262. The ALLMOTI5 search motif identifies three regions, including amino acid residues 116-184, 228-269 and 452-500. Three regions containing proline residues followed by a leucine zipper-like sequence were found beginning at proline residues 214, 286 and 451.

The Lupas program identified two regions it predicted had potential for coiled-coil structure, which include amino acid residues 141-172 and 444-483.

22. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP178/DP107 ANALOGS IN HEPATITIS B VIRUS

FIG. 35 depicts the results of a PZIP motif search conducted on the Hepatitis B virus subtype AYW. Two regions of interest within the major surface antigen precursor S protein were identified. The first lies just C-terminal to the proposed fusion peptide of the major surface antigen (Hbs) which is found at amino acid residues 174-191. The second region is located at amino acid residues 233-267. The Lupas program predicts no coiled-coil repeat regions.

In order to test the potential anti-HBV antiviral activity of these D178/DP107 analog regions, peptides derived from area around the analog regions are synthesized, as shown in FIG. 52A-B. These peptides represent one amino acid peptide "walks" through the putative DP178/DP107 analog regions. The peptides are

synthesized according to standard Fmoc chemistry on Rinkamide MBHA resins to provide for carboxy terminal blockade (Chang, C.D. and Meinhofer, J., 1978, Int. J. Pept. Protein Res. 11:246-249; Fields, G.B. and Noble, R.L., 1990, Int. J. Pept. Protein Res. 35:161-214). Follwing complete synthesis, the peptide amino-terminus is blocked through automated acetylation and the peptide is cleaved with trifluoroacetic acid (TFA) and the appropriate scavengers (King, D.S. et al., 1990, Int. J. Pept. Res. 36:255-266). After cleavage, the peptide is precipitated with ether and dried under vacuum for 24 hours.

The anti-HBV activity of the peptides is tested by utilizing standard assays to determine the test peptide concentration required to cause an acceptable (e.g., 90%) decrease in the amount of viral progeny formed by cells exposed to an HBV viral inoculum. Candidate antivial peptides are further characterized in model systems such as wood chuck tissue culture and animal sytems, prior to testing on humans.

23. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP178/DP107 ANALOGS IN SIMIAN MASON-PFIZER MONKEY VIRUS

The results depicted herein illustrate the results of search motifs conducted on the Simian Mason-Pfizer monkey virus. The motifs reveal DP178/DP107 analogs within the enveloped (TM) protein GP20, as shown in FIG. 36.

The 107x178x4 motifs identifies a region at amino acid residues 422-470. The ALLMOTI5 finds a region at amino acid residues 408-474. The Lupas program predicted a coiled-coil structure a amino acids 424-459.

24. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP178/DP107 ANALOGS IN BACTERIAL PROTEINS

The results presented herein demonstrate the identification of DP178/DP107 analogs corresponding to sequences present in proteins of a variety of bacterial species.

FIG. 37 depicts the search motif results for the Pseudomonas aeruginosa fimbrial protein (Pilin). Two regions were identified by motifs 107x178x4 and ALLMOTI5. The regions located at amino acid residues 30-67 and 80-144 were identified by the 107x178x4 motif. The regions at amino acid residues 30-68 and 80-125 were identified by the ALLMOTI5.

FIG. 38 depicts the search motif results for the Pseudomonas gonorrhoeae fimbrial protein (Pilin). A single region was identified by both the 107x178x4 and the ALLMOTI5 motifs. The region located at amino acid residues 66-97 was identified by the 107x178x4 motif. The region located at amino acid residues 66-125 were identified by the ALLMOTI5 search motif. No coiled-coil regions were predicted by the Lupas program.

FIG. 39 depicts the search motif results for the Hemophilus Influenza fimbrial protein (Pilin). A single region was identified by both the 107x178x4 and the ALLMOTI5 motifs. The region located at amino acid residues 102-129 was identified by the 107x178x4 motif. The region located at amino acid residues 102-148 were identified by the ALLMOTI5 search motif. No coiled-coil regions were predicted by the Lupas program.

FIG. 40 depicts the search motif results for the Staphylococcus aureus toxic shock syndrome Hemophilus Influenza fimbrial protein (Pilin). A single region

was identified by both the 107x178x4 and the ALLMOTI5 motifs. The region located at amino acid residues 102-129 was identified by the 107x178x4 motif. The region located at amino acid residues 102-148 were identified by the ALLMOTI5 search motif. No coiled-coil regions were predicted by the Lupas program.

FIG. 41 summarizes the motif search results conducted on the Staphylococcus aureus enterotoxin Type E protein. These results demonstrate the successful identification of DP178/DP107 analogs corresponding to peptide sequences within this protein, as described below.

The ALLMOTI5 motif identified a region at amino acid residues 22-27. The 107x178x4 motif identified two regions, with the first at amino acid residues 26-69 and the second at 88-115. A P12LZIPC motif search identified two regions, at amino acid residues 163-181 and 230-250.

The Lupas program predicted a region with a high propensity for coiling at amino acid residues 25-54. This sequence is completely contained within the first region identified by both ALLMOTI5 and 107x178x4 motifs.

FIG. 42 depicts the search motif results conducted on a second Staphylococcus aureus toxin, enterotoxin A. Two regions were identified by the ALLMOTI5 motif, at amino acid residues 22-70 and amino acid residues 164-205. The 107x178x4 motif found two regions, the first at amino acid residues 26-69 and the second at amino acid residues 165-192. A P23LZIPC motif search revealed a region at amino acid residues 216-250. No coiled-coil regions were predicted by the Lupas program.

FIG. 43 shows the motif search results conducted on the E. coli heat labile enterotoxin A protein, demonstrating that identification of DP178/DP107 analogs corresponding to peptides located within this protein. Two regions were identified by the ALLMOTI5 motif, with the first residing at amino acid residues 55-115, and the second residing at amino acid residues 216-254. The 107x178x4 motif identified a single region at amino acid residues 78-105. No coiled-coil regions were predicted by the Lupas program.

25. EXAMPLE: COMPUTER-ASSISTED IDENTIFICATION OF DP178/DP107 ANALOGS WITHIN VARIOUS HUMAN PROTEINS

The results presented herein demonstrate the identification of DP178/DP107 analogs corresponding to peptide sequences present within several different human proteins.

FIG. 44 illustrates the search motif results conducted on the human c-fos oncoprotein. The ALLMOTI5 motif identified a single region at amino acid residues 155-193. The 107x178x4 motif identified one region at amino acid residues 162-193. The Lupas program predicted a region at amino acid residues 148-201 to have coiled-coil structure.

FIG. 45 illustrates the search motif results conducted on the human lupus KU autoantigen protein P70. The ALLMOTI5 motif identified a single region at amino acid residues 229-280. The 107x178x4 motif identified one region at amino acid residues 235-292. The Lupas program predicted a region at amino acid residues 232-267 to have coiled-coil structure.

FIG. 46 illustrates the search motif results conducted on the human zinc finger protein 10. The

ALLMOTI5 motif identified a single region at amino acid residues 29-81. The 107x178x4 motif identified one region at amino acid residues 29-56. A P23LZIPC motif search found a single region at amino acid residues 420-457. The Lupas program predicted no coiled-coil regions.

26. EXAMPLE: POTENTIAL MEASLES VIRUS DP178/DP107 ANALOGS: CD AND ANTIVIRAL CHARACTERIZATION

In the Example presented herein, measles (MeV) virus DP178-like peptides identified by utilizing the computer-assisted search motifs described in the Examples presented in Sections 9 and 21, above, are tested for anti-MeV activity. Additionally, circular dichroism (CD) structural analyses are conducted on the peptides, as discussed below. It is demonstrated that several of the identified peptides exhibit potent antiviral capability. Additionally, it is shown that none of the these peptides exhibit a substantial helical character.

26.1 MATERIALS AND METHODS

Structural analyses: The CD spectra were measured in a 10mM sodium phosphate, 150mM sodium chloride, pH 7.0, buffer at approximately 10mM concentrations, using a 1 cm pathlength cell on a Jobin/Yvon Autodichrograph Mark V CD spectrophotometer. Peptide concentrations were determined from A_{280} using Edlehoch's method (1967, Biochemistry 6:1948).

Anti-MeV antiviral activity syncytial reduction assay: The assay utilized herein tested the ability of the peptides to disrupt the ability of Vero cells

acutely infected with MeV (i.e., cells which are infected with a multiplicity of infection of 2-3) to fuse and cause syncytial formation on a monolayer of an uninfected line of Vero cells. The more potent the peptide, the lower the observed level of fusion, the greater the antiviral activity of the peptide.

Uninfected confluent monolayers of Vero cells were grown in microtiter wells in 10% FBS EMEM (Eagle Minimum Essential Medium w/o L-glutamine [Bio Whittaker Cat. No. 12-125F], with fetal bovine serum [FBS; which had been heat inactivated for 30 minutes at 56°C; Bio Whittaker Cat. No. 14-501F) supplemented at 10%, antibiotics/antimycotics (Bio Whittaker Cat. No. 17-602E) added at 1%, and glutamine added at 1%.

To prepare acutely infected Vero cells for addition to the uninfected cells, cultures of acutely infected Vero cells were washed twice with HBSS (Bio Whittaker Cat. No. 10-543F) and cell monolayers were removed with trypsin (Bio Whittaker Cat. No. 17-161E). Once cells detached, media was added, any remaining clumps of cells were dispersed, and hemacytometer cell counts were performed.

The antiviral assay was conducted by, first, removing all media from the wells containing uninfected Vero cells, then adding peptides (at the dilutions described below) in 10% FBS EMEM, and 50-100 acutely MeV-infected Vero cells per well. Wells were then incubated at 37°C for a maximum of 18 hours.

On day 2, after cells in control wells were checked for fusion centers, media was removed from the wells, followed by addition, to each well, of approximately 50µl 0.25% Crystal Violet stain in methanol. Wells were rinsed twice with water immediately, to remove excess stain and were then

allowed to dry. The number of syncytia per well were then counted, using a dissecting microscope.

Anti-MeV antiviral activity plaque reduction assay: The assay utilized herein tested the ability of the peptides to disrupt the ability of MeV to infect permissive, uninfected Vero cells, leading to the infected cells' fusing with uninfected cells to produce syncytia. The lower the observed level of syncytial formation, the greater the antiviral activity of the peptide.

Monolayers of uninfected Vero cells are grown as described above.

The antiviral assay was conducted by, first, removing all media from the wells containing uninfected Vero cells, then adding peptides (at the dilutions described below) in 10% FBS EMEM, and MeV stock virus at a final concentration of 30 plaque forming units (PFU) per well. Wells were then incubated at 37°C for a minimum of 36 hours and a maximum of 48 hours.

On day 2, after cells in control wells were checked for fusion centers, media was removed from the wells, followed by addition, to each well, of approximately 50μl 0.25% Crystal Violet stain in methanol. Wells were rinsed twice with water immediately, to remove excess stain and were then allowed to dry. The number of syncytia per well were then counted, using a dissecting microscope.

Peptides: The peptides characterized in the study presented herein were peptides T-252A0 to T-256A0, T-257B1/C1, and T-258B1 to T-265B0, and T-266A0 to T-268A0, as shown in FIG. 47. These peptides represent a walk through the DP178-like region of the MeV fusion protein.

Each peptide was tested at 2-fold serial dilutions ranging from 100μg/ml to approximately 100ng/ml. For each of the assays, a well containing no peptide was also used.

26.2 RESULTS

The data summarized in FIG. 47 represents antiviral and structural information obtained via "peptide walks" through the DP178-like region of the MeV fusion protein.

As shown in FIG. 47, the MeV DP178-like peptides exhibited a range of antiviral activity as crude peptides. Several of these peptides were chosen for purification and further antiviral characterization. The IC_{50} values for such peptides were determined, as shown in FIG. 47, and ranged from 1.35μg/ml (T-257B1/C1) to 0.072μg/ml (T-265B1). None of the DP178-like peptides showed, by CD analysis, a detectable level of helicity.

Thus, the computer assisted searches described, hereinabove, as in for example, the Example presented in Section 9, for example, successfully identified viral peptide domains that represent highly promising anti-MeV antiviral compounds.

27. EXAMPLE: POTENTIAL SIV DP178/DP107 ANALOGS: ANTIVIRAL CHARACTERIZATION

In the Example presented herein, simian immunodeficiency virus (SIV) DP178-like peptides identified by utilizing the computer-assisted search motifs described in the Examples presented in Sections 9, 12 and 19, above, were tested for anti-SIV activity. It is demonstrated that several of the

identified peptides exhibit potent antiviral capability.

27.1 MATERIALS AND METHODS

Anti-SIV antiviral assays: The assay utilized herein were as reported in Langolis et al. (Langolis, A.J. et al., 1991, AIDS Research and Human Retroviruses 7:713-720).

Peptides: The peptides characterized in the study presented herein were peptides T-391 to T-400, as shown in FIG. 48. These peptides represent a walk through the DP178-like region of the SIV TM protein.

Each peptide was tested at 2-fold serial dilutions ranging from 100μg/ml to approximately 100ng/ml. For each of the assays, a well containing no peptide was also used.

27.2 RESULTS

The data summarized in FIG. 48 represents antiviral information obtained via "peptide walks" through the DP178-like region of the SIV TM protein.

As shown in FIG. 48, peptides T-391 to T-400 were tested and exhibited a potent antiviral activity as crude peptides.

Thus, the computer assisted searches described, hereinabove, as in for example, the Example presented in Section 9, for example, successfully identified viral peptide domains that represent highly promising anti-SIV antiviral compounds.

28. EXAMPLE: ANTI-VIRAL ACTIVITY OF DP107 AND DP-178 PEPTIDE TRUNCATIONS AND MUTATIONS

The Example presented in this Section represents a study of the antiviral activity of DP107 and DP178

truncations and mutations. It is demonstrated that several of these DP107 and DP178 modified peptides exhibit substantial antiviral activity.

28.1 MATERIALS AND METHODS

Anti-HIV assays: The antiviral assays performed were as those described, above, in Section 6.1. Assays utilized HIV-1/IIIb and/or HIV-2 NIHZ isolates. Purified peptides were used, unless otherwise noted in FIGS. 49A-C.

Peptides: The peptides characterized in the study presented herein were:

1) FIGS. 49A-C present peptides derived from the region around and containing the DP178 region of the HIV-1 BRU isolate. Specifically, this region spanned from gp41 amino acid residue 615 to amino acid residue 717. The peptides listed contain truncations of this region and/or mutations which vary from the DP178 sequence amino acid sequence. Further, certain of the peptides have had amino- and/or carboxy-terminal groups either added or removed, as indicated in the figures; and

2) FIG. 50. presents peptides which represent truncations of DP107 and/or the gp41 region surrounding the DP107 amino acid sequence of HIV-1 BRU isolate. Certain of the peptides are unblocked or biotinylated, as indicated in the figure.

Blocked peptides contained an acyl N-terminus and an amido C-terminus.

28.2 RESULTS

Anti-HIV antiviral data was obtained with the group 1 DP178-derived peptides listed in FIG. 49A-C. The full-length, non-mutant DP178 peptide (referred to in FIG. 49A-C as T20) results shown are for 4ng/ml.

In FIG. 49A, a number of the DP178 truncations exhibited a high level of antiviral activity, as evidenced by their low IC_{50} values. These include, for example, test peptides T-50, T-624, T-636 to T-641, T-645 to T-650, T-652 to T-654 and T-656. T-50 represents a test peptide which contains a point mutation, as indicated by the residue's shaded background. The HIV-1-derived test peptides exhibited a distinct strain-specific antiviral activity, in that none of the peptides tested on the HIV-2 NIHZ isolate demonstrated appreciable antti-HIV-2 antiviral activity.

Among the peptides listed in FIG. 49B, are test peptides representing the amino (T-4) and carboxy (T-3) terminal halves of DP178 were tested. The amino terminal peptide was not active (IC_{50}>400μg/ml) whereas the carboxy terminal peptide showed potent antiviral activity (IC_{50}= 3μg/ml). A number of additional test peptides also exhibited a high level of antiviral activity. These included, for example, T-61/T-102, T-217 to T-221, T-235, T-381, T-677, T-377, T-590, T-378, T-591, T-271 to T-272, T-611, T-222 to T-223 and T-60/T-224. Certain of the antiviral peptides contain point mutations and/or amino acid residue additions which vary from the DP178 amino acid sequence.

In FIG. 49C, point mutations and/or amino and/or carboxy-terminal modifications are introduced into the DP178 amino acid sequence itself. As shown in the

figure, the majority of the test peptides listed exhibit potent antiviral activity.

Truncations of the DP107 peptide (referred to in IG. 50 as T21) were also produced and tested, as shown in FIG. 50. FIG. 50 also presents data concerning blocked and unblocked peptides which contain additional amino acid residues from the gp41 region in which the DP107 sequence resides. Most of these peptides showed antiviral activity, as evidenced by their low IC_{50} values.

Thus, the results presented in this Section demonstrate that not only do the full length DP107 and DP178 peptides exhibit potent antiviral activity, but truncations and/or mutant versions of these peptides can also possess substantial antiviral character.

29: EXAMPLE: POTENTIAL EPSTEIN-BARR DP178/DP107 ANALOGS: ANTIVIRAL CHARACTERIZATION

In the Example presented herein, peptides derived from the Epstein-Barr (EBV) DP-178/DP107 analog region of the Zebra protein identified, above, in the Example presented in Section 20 are described and tested for anti-EBV activity. It is demonstrated that among these peptides are ones which exhibit potential anti-viral activity.

29.1 MATERIALS AND METHODS

Electrophoretic Mobility Shift Assays (EMSA): Briefly, an EBV Zebra protein was synthesized utilizing SP6 RNA polymerase in vitro transcription and wheat germ in vitro translation systems (Promega Corporation recommendations; Butler, E.T. and Chamberlain, M.J., 1984, J. Biol. Chem. 257:5772; Pelham, H.R.B. and Jackson, R.J., 1976, Eur. J.

Biochem. 67:247). The in vitro translated Zebra protein was then preincubated with increasing amounts of peptide up to 250 ng/ml prior to the addition of 10,000 to 20,000 c.p.m. of a ^{32}P-labeled Zebra response element DNA fragment. After a 20 minute incubation in the presence of the response element, the reaction was analyzed on a 4% non-denaturing polyacrylamide gel, followed by autoradiography, utilizing standard gel-shift procedures. The ability of a test peptide to prevent Zebra homodimer DNA binding was assayed by the peptide's ability to abolish the response element gel migration retardation characteristic of a protein-bound nucleic acid molecule.

Peptides: The peptides characterized in this study represent peptide walks through the region containing, and flanked on both sides by, the DP178/DP107 analog region identified in the Example presented in Section 20, above, and shown as shown in FIG. 33. Specifically, the peptide walks covered the region from amino acid residue 173 to amino acid residue 246 of the EBV Zebra protein.

Each of the tested peptides were analyzed at a range of concentrations, with 150ng/ml being the lowest concentration at which any of the peptides exerted an inhibitory effect.

29.2 RESULTS

The EBV Zebra protein transcription factor contains a DP178/DP107 analog region, as demonstrated in the Example presented, above, in Section 20. This protein appears to be the primary factor responsible for the reactivation capability of the virus. A method by which the DNA-binding function of the Zebra virus may be abolished may, therefore, represent an

effective antiviral technique. In order to identify potential anti-EBV DP178/DP107 peptides, therefore, peptides derived from the region identified in Section 20, above, were tested for their ability to inhibit Zebra protein DNA binding.

The test peptides' ability to inhibit Zebra protein DNA binding was assayed via the EMSA assays described, above, in Section 28.1. The data summarized in FIG. 51A-B presents the results of EMSA assays of the listed EBV test peptides. These peptides represent one amino acid "walks" through the region containing, and flanked on both sides by, the DP178/DP107 analog region identified in the Example presented in Section 20, above, and shown as shown in FIG. 33. As shown in FIG. 51A-B, the region from which these peptides are derived lies from EBV Zebra protein amino acid residue 173 to 246. A number of the test peptides which were assayed exhibited an ability to inhibit Zebra protein homodimer DNA binding, including 439, 441, 444 and 445.

Those peptides which exhibit an ability to inhibit Zebra protein DNA binding represent potential anti-EBV antiviral compounds whose ability to inhibit EBV infection can be further characterized.

30. EXAMPLE: IDENTIFICATION OF RSV DP107/DP178 ANALOGS WITH REDUCED BINDING AFFINITY

In the example presented herein, peptides derived from the RSV DP178 analog T112 are described and tested for binding affinity to the DP107-like domain of the RSV F1-protein. Particular peptides are identified that have a reduced binding affinity for their DP107-like target, and key amino acid residues

are identified the confer high binding affinity to the native peptide (*i.e.*, to T112). Such peptides are useful, *e.g.*, in screening assays such as those described above in Section 5.6.1 to identify compounds which inhibit or disrupt the interaction between DP107 and DP178, and in providing guidance for generation of additional peptides exhibiting reduced affinity binding.

30.1 MATERIALS AND METHODS

A maltose binding fusion protein of the RSV F1-protein (MF5.1) was constructed using methods similar to those described in Section 8.1.2, *supra*, for construction of the M41 fusion protein. Specifically, the DNA sequence corresponding amino acid residues 142-302 of the RSV F1 protein was amplified by PCR and cloned into the Xmn I site of the expression vector pMal-p2 (New England Biolab) to give MF5.1. These amino acid residues correspond to the extracellular domain of the RSV F1 protein including its DP107 region but excluding the DP178 region.

The peptides characterized in the study presented herein were: T122, T800, T801, T802, T803, T804, T805, T806, T807, T808, T809, T810, T811, T1669, T1670, T1671, T1672, T1673, T1680, T1681, T1682, T1683 and T1684, as shown in FIG. 53. T112 represents the DP178-like region of the RSV F1 protein. The other peptides characterized are modified DP178 proteins derived from T112.

Cell fusion assays were performed with each of the peptides as described in Section 17 above. The binding affinity of each peptide was also measured in a competitive binding assay described in Section 5.6.1

above, wherein the concentration of each peptide necessary to bind to the M5.1 fusion protein (*i.e.*, the B_{50} value), and thereby disrupt binding of biotin labeled T112 (T888) to the fusion protein, was measured.

30.2 RESULTS

T112 is a 35 amino acid residue peptide that corresponds to amino acid residues 482-516 of the RSV F1 protein and has the following amino acid sequence:

VFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV

The peptide represents the DP178-like region of the RSV F1 protein and has substantial antiviral activity against RSV as discussed in Section 17.2 above and shown in FIG. 28A.

T112 analogs were generated according to at least three different strategies to generate peptides based on T112 that would still bind to the DP107-like domain of the RSV F1 protein but with a lower binding affinity. First, a truncated peptide was generated, reducing the length of the peptide from 35 to 28 amino acid residues. Specifically, the truncated peptide, which is referred to herein as T67, had the amino acid sequence:

DEFDASISQVNEKINQSLAFIRKSDELL

corresponding to amino acid residues 486-213 of the F1 fusion protein. The binding affinity of the peptide to the DP107-like domain of F1 protein was determined according to the methods described in Section 5.6.1

above. The truncated peptide had a binding affinity (5 nM) that was five times lower than that of the full length T112 peptide (2 nM).

As part of a second strategy, the peptides identified as T800 through T811 in FIG. 53 were synthesized to identify particular amino acids in T112 that contribute to a larger part of that peptide's binding affinity. As a whole, these alanine substitutions represent an "alanine-scanning" type walk across the sequence of T112.

Each of the peptides synthesized had a change of three consecutive amino acid residues in the T112 sequence to three alanine residues. Each peptide was tested for its ability to inhibit the binding of the native peptide (*i.e.*, of T112) in a competitive binding assay as described in Section 5.6.1 above. The results are also shown in FIG. 53. In particular, the peptides T802, T804, T807 and T810 had significantly reduced affinity for the DP107-like target, suggesting that the regions containing amino acid residues 488-490, 494-496, 503-505 and 512-514 of the RSV F1 protein (amino acid residues 7-9, 13-15, 22-24 and 31-33, respectively, of T112), contribute significantly to the high binding affinity of T112 for its DP107-like target in the RSV F1 protein.

The peptides T1669-T1673 and T1680 through T1684 were then synthesized, each of which contains a single alanine substitution at one of the above-listed amino acid residue positions of T112. The binding affinity of these peptides for their DP107-like target can also be determined by means of the same routine screening assays, thereby identifying individual amino acid residues which affect binding affinity of T112.

In addition, an additional novel peptide, referred to as T786, was generated by modifying various amino acid residues in the T112 sequence which were identified, using standard principles of protein and design, as affecting properties such as binding affinity, solubility and biological stability. Specifically the following amino acid residue substitutions were made: F_2 - Y, S_{21} - A, F_{24} - Y and S_{28} - A, wherein the subscript numerals indicate the amino acid residue position in T112. The resultant peptide, which is referred to herein as T786, thus had the amino acid sequence:

VYPSDEFDASISQVNEKINQALAYIRKADELLHNV

The binding affinity of this novel peptide for the DP107 target was found to be 19 nM, *i.e.*, approximately ten-fold less than the binding affinity of T112.

The data demonstrates that peptides having a reduced binding affinity for a DP107 target (*i.e.*, for an HR1 domain) may be readily found by modifying a DP178 peptide such as T112, *e.g.*, by means of the routine techniques and assays described herein. Further, the techniques and assays identify key amino acid residues which may be used to construct and identify other reduced affinity peptides.

31. EXAMPLE: IDENTIFICATION OF HIV DP107/DP178 ANALOGS WITH REDUCED BINDING AFFINITY

In the example presented herein, peptides derived from DP178, which is also referred to as T20, are described and tested for binding affinity to the DP107

domain of the HIV gp41. Particular peptides are identified that have a reduced binding affinity for their DP107 target, and key amino acid residues are identified the confer high binding affinity to the native peptide (*i.e.*, to T20). Such peptides are useful, *e.g.*, in screening assays such as those described above in Section 5.6.1 to identify compounds which inhibit or disrupt the interaction between DP107 and DP178.

Specifically, the peptides identified as T813 and T868 through T878 in FIG. 53 were synthesized to identify particular amino acids in T20 (DP178) that contribute to a greater part of that peptide's binding affinity. Each of the peptides synthesized had a change of three consecutive amino acid residues in the T20 sequence to three alanine residues. The antiviral activity of each peptide was assayed in cell fusion assays as described in Section 6.1.3, above. The binding affinities of the peptides were also measured in a competitive binding assay described in Section 5.6.1 above, wherein each peptides ability to disrupt the binding of either biotin (T83) or fluorescein (T1342) labeled DP178 (T20) to the M41Δ178 fusion protein described in Section 8, above, was measured. The binding affinity of each peptide to the peptide referred to as T764 (GSTMGARSMTLTVQARQLLSGIVQQNNLLRAIEAQQH) also measured using circular dichroism to monitor the amount of secondary structure (*i.e.*, helicity) adopted by the peptides. T764 is a peptide which represents the DP107 target domain of DP178 (T20).

The results are provided in FIG. 54. In particular, the peptides T813, T878, T874-T876 and

T871 have significantly reduced affinity for the DP107 region, suggesting the regions corresponding to the substituted amino acid residues in those peptides contribute significantly to the high binding affinity of T20. The peptides T1627-T1632, T1650-T1653 and T1656-T1665 were then synthesized. Each of these peptides contains a single alanine substitution at one of the amino acid residues in one of the regions identified as contributing significantly to the high binding affinity of T20. Identical assays which measured the binding affinity of these peptides identified four essential residues (I_{646}, Q_{652}, Q_{653} and N_{656}, with the subscript numerals indicating the residue position in the HIV-1_{LAI} gp41 amino acid sequence) in which alanine-substitution completely prevented binding to the DP107 domain, as well as five residues (L_{641}, I_{642}, I_{645}, E_{657} and L_{663}, with the subscript numerals indicating the residue) in which alanine-substitution position in the HIV-1_{LAI} gp41 amino acid sequence) that reduced the binding affinity but did not actually block binding to the DP107 domain.

The data demonstrates that peptides having a reduced binding affinity for a DP107 target (*i.e.*, for an HR1 domain) may be readily found by modifying a DP178 peptide such as T20, *e.g.*, by means of the routine techniques and assays described herein. Further, the techniques and assays identify key amino acid residues which may be used to construct and identify other reduced affinity peptides.

The present invention is not to be limited in scope by the specific embodiments described which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method for identifying a compound that inhibits the formation of or disrupts a DP107/DP178 complex comprising:

(a) preparing, both in the presence and in the absence of a test compound, a reaction mixture containing a DP107 peptide and a DP178 peptide under conditions and for a time sufficient to allow formation of a DP107/DP178 complex; and

(b) detecting the formation of a DP107/DP178 complex both in the presence and in the absence of the test compound,

wherein the formation of a DP107/DP178 complex in the absence, but not in the presence of the test compound indicates that the compound inhibits the formation of or disrupts a DP107/DP178 complex.

2. The method of Claim 1, wherein the DP107 peptide or the DP178 peptide is a modified DP107 or DP178 peptide.

3. The method of Claim 2 wherein the modified DP107 or DP178 peptide has a reduced binding affinity.

HIV1LAI	(DP-178; SEQ ID:1)	YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF
HIV1SF2	(DP-185; SEQ ID:3)	YTNTIYNLLEESQNQQEKNEQELLELDKWASLWNWF
HIV1RF	(SEQ ID:4)	YTGIIYNLLEESQNQQEKNEQELLELDKWANLWNWF
HIV1MN	(SEQ ID:5)	YTSLIYSLLEKSQTQQEKNEQELLELDKWASLWNWF
HIV2ROD	(SEQ ID:6)	LEANISKSLEQAQIQQEKNMYELQKLNSWDIFGNWF
HIV2NIHZ	(SEQ ID:7)	LEANISQSLEQAQIQQEKNMYELQKLNSWDVFTNWL
DP180	(SEQ ID:2)	SSESFTLLEQWNNWKLQLAEQWLEQINEKHYLEDIS
DP118	(SEQ ID:10)	QQLLDVVKRQQEMLRLTVWGTKNLQARVTAIEKYLKDQ
DP125	(SEQ ID:8)	CGGNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ
DP116	(SEQ ID:9)	LQARILAVERYLKDQQQ

FIG.1

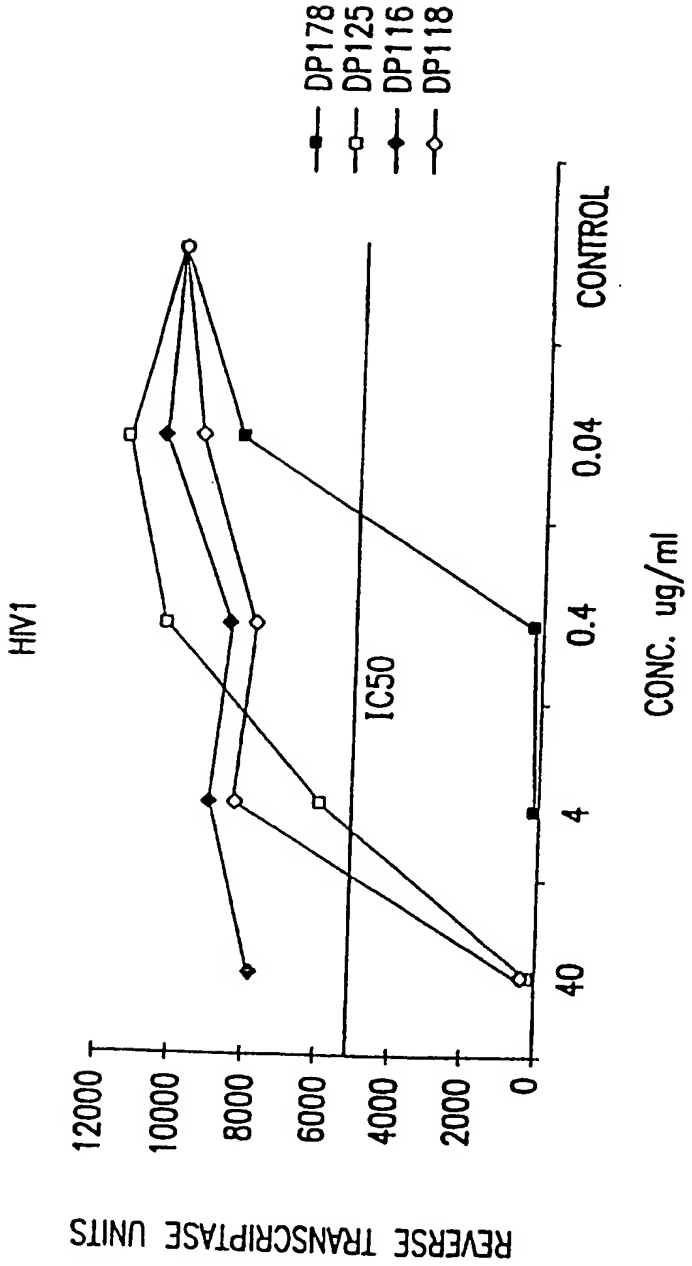


FIG.2

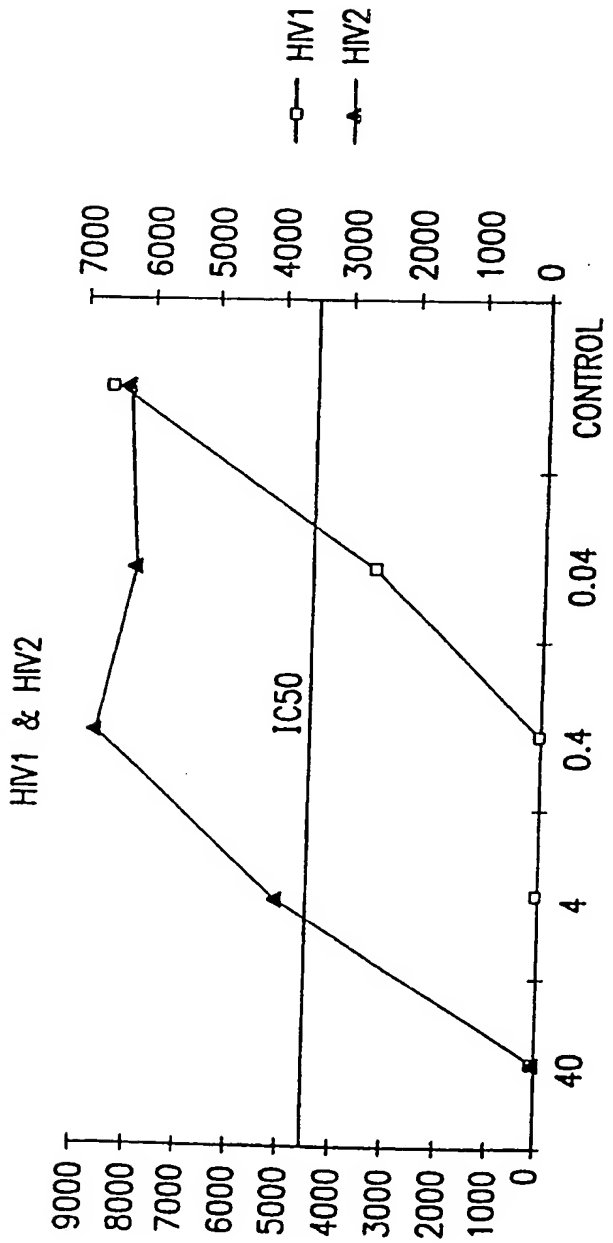


FIG.3

Number of Syncytia/well: concentration in μg/ml (micrograms/ml)

DP178	10	5	1	0.2	0.1	0.05	0.025	0.0125	Control
Syncytia									
HIV1LAI	0	0	0	0	0	0	0	0	67
HIV1MN	0	0	0	0	0	ND	ND	ND	34
HIV1RF	0	0	0	0	0	ND	ND	ND	65
HIV1SF2	0	0	0	0	0	ND	ND	ND	58

DP125	10	5	1	0.2	0.1	0.05	0.025	0.0125	Control
Syncytia									
HIV1LAI	0	0	54	69	80	75	79	82	67
HIV1MN	0	0	30	36	ND	ND	ND	ND	34
HIV1RF	0	0	67	63	ND	ND	ND	ND	65
HIV1SF2	0	0	9	66	ND	ND	ND	ND	58

DP116	10	5	1	0.2	0.1	0.05	0.025	0.0125	Control
Syncytia									
HIV1LAI	75	ND	ND	ND	ND	ND	ND	ND	67
HIV1MN	35	ND	ND	ND	ND	ND	ND	ND	34
HIV1RF	81	ND	ND	ND	ND	ND	ND	ND	65
HIV1SF2	81	ND	ND	ND	ND	ND	ND	ND	58

FIG.4A

DP180	40	20	10	5	2.5	1.25	0.625	0.3125	Control
Syncytia									
HIV1LAI	50	>45	>45	>45	>45	>45	>45	>45	58

DP185	40	20	10	5	2.5	1.25	0.625	0.3125	Control
Syncytia									
HIV1LAI	0	0	0	0	0	0	0	ND	60

FIG.4B

HIV1

	Number of Syncytia/well: concentration in ng/ml (nanograms/ml)							
DP178	20	10	5	2.5	1.25	0.625	0.3125	Control
Syncytia HIV1	0	0	0	0	0	14	20	48
DP116	20	10	5	2.5	1.25	0.625	0.3125	Control
Syncytia HIV1	ND	48	ND	ND	ND	ND	ND	ND

HIV2

	Number of Syncytia/well: concentration in μg/ml (micrograms/ml)							
DP178	20	10	5	2.5	1.25	0.625	0.3125	Control
Syncytia HIV2	50	54	55	57	63	77	78	76
DP116	20	10	5	2.5	1.25	0.625	0.3125	Control
Syncytia HIV2	ND	58	ND	ND	ND	ND	ND	ND

FIG.5

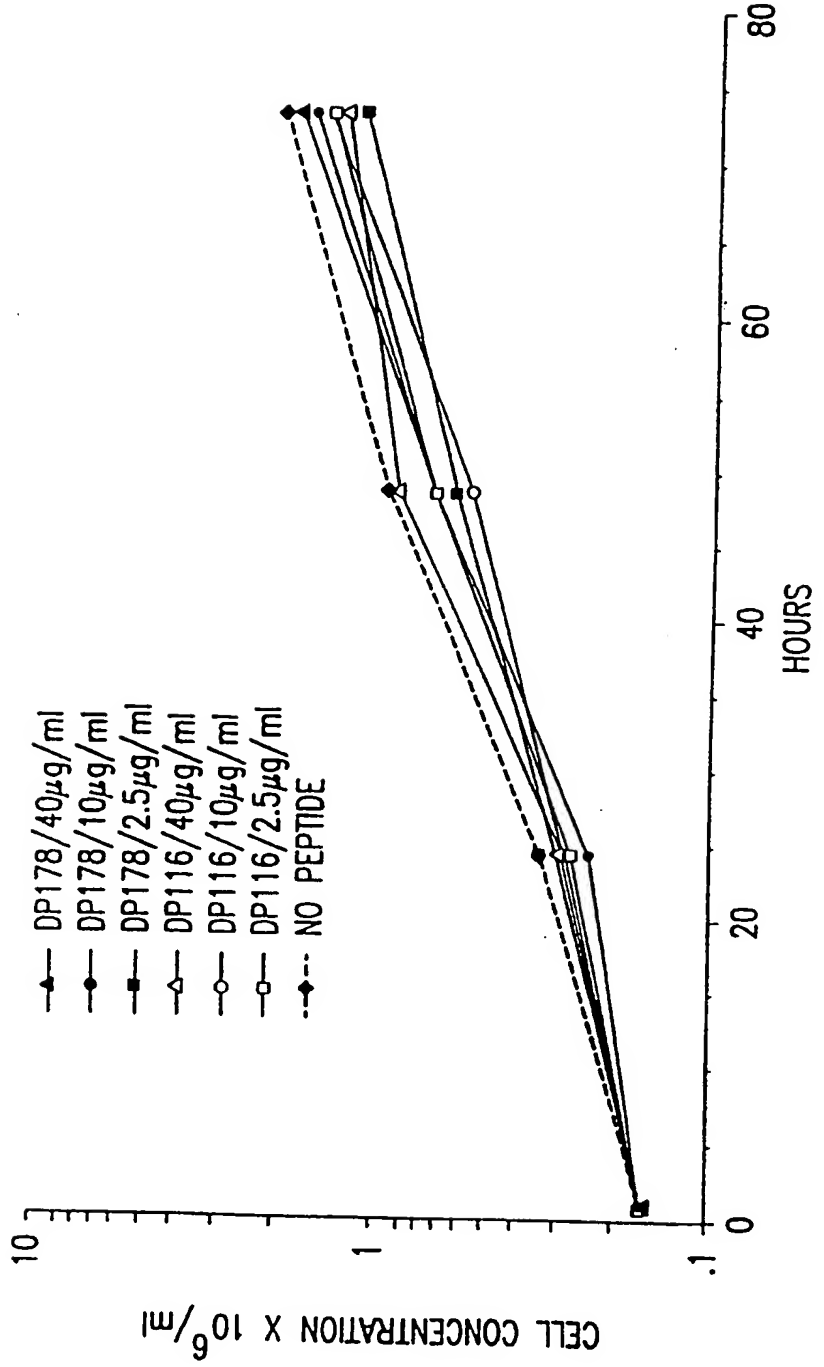


FIG.6

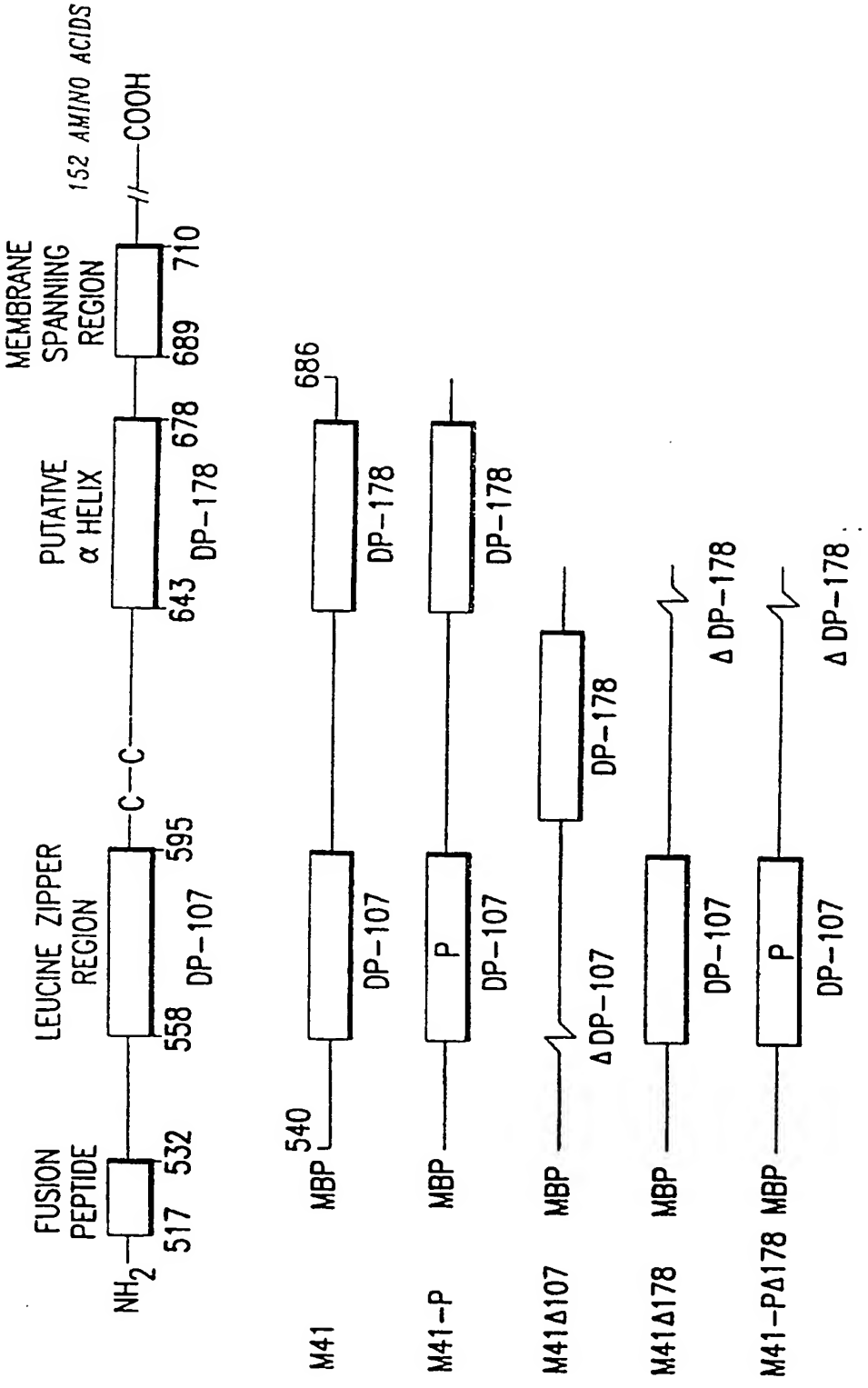


FIG.7

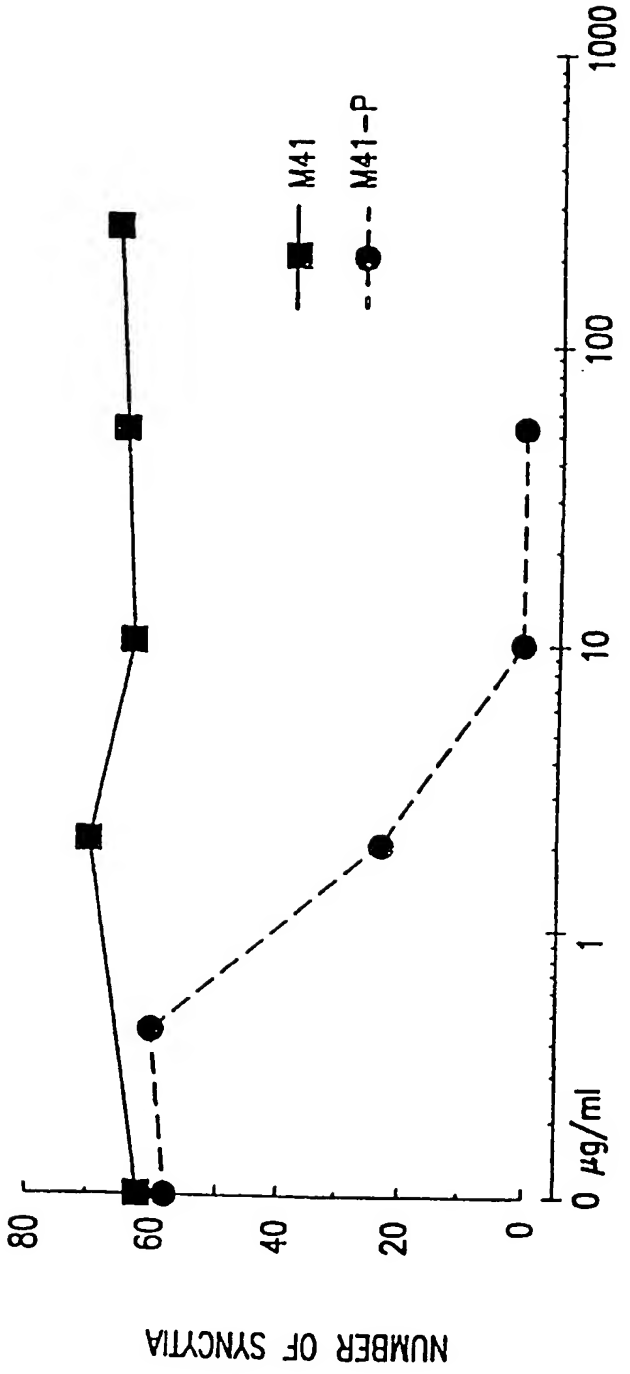


FIG.8

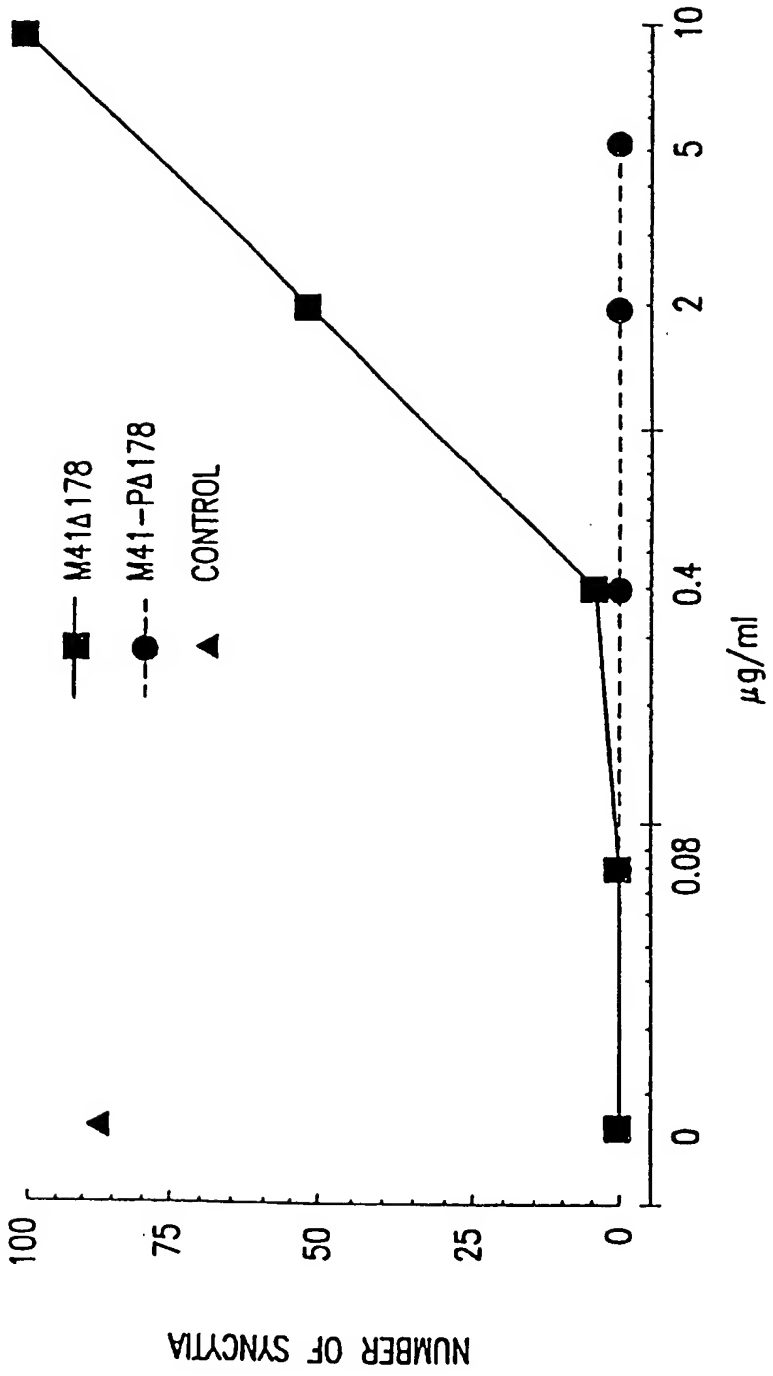


FIG.9

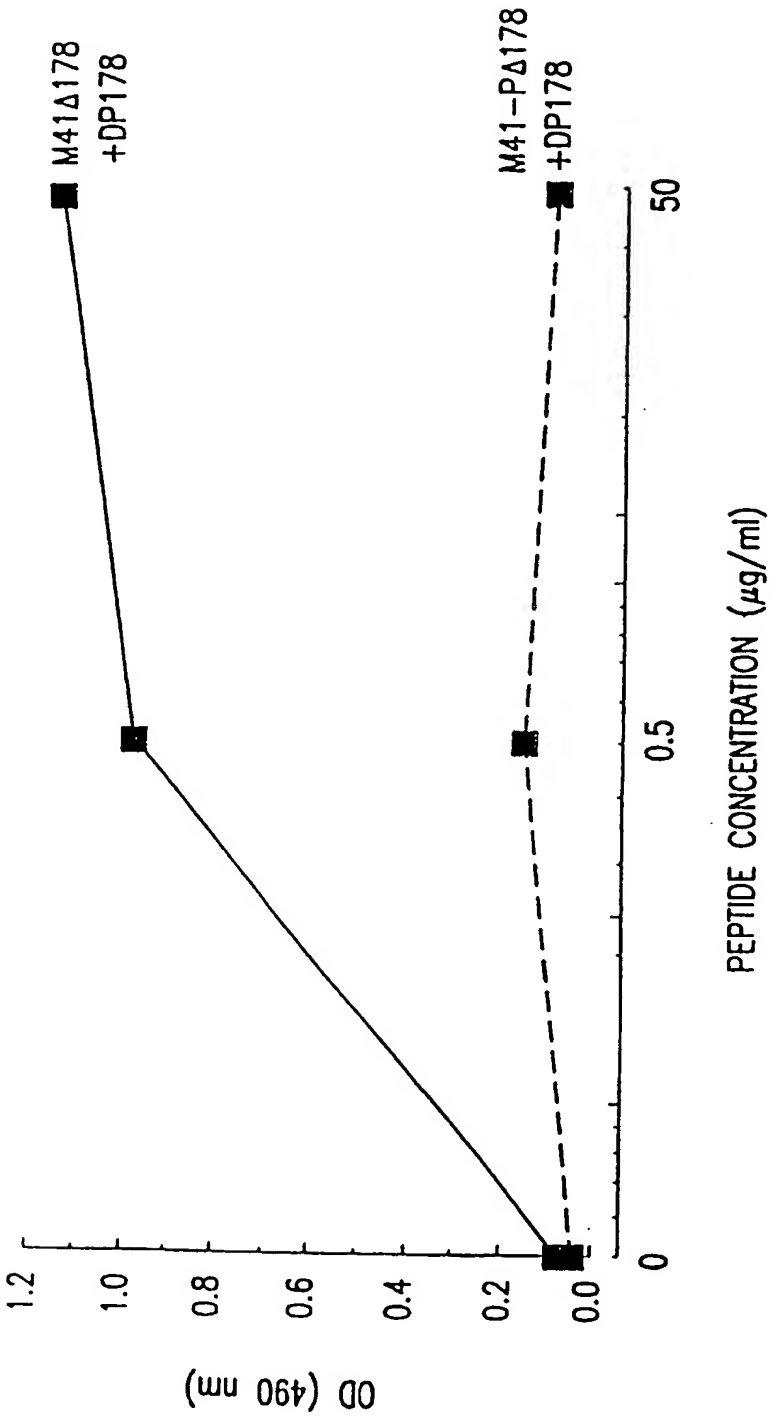


FIG. 10

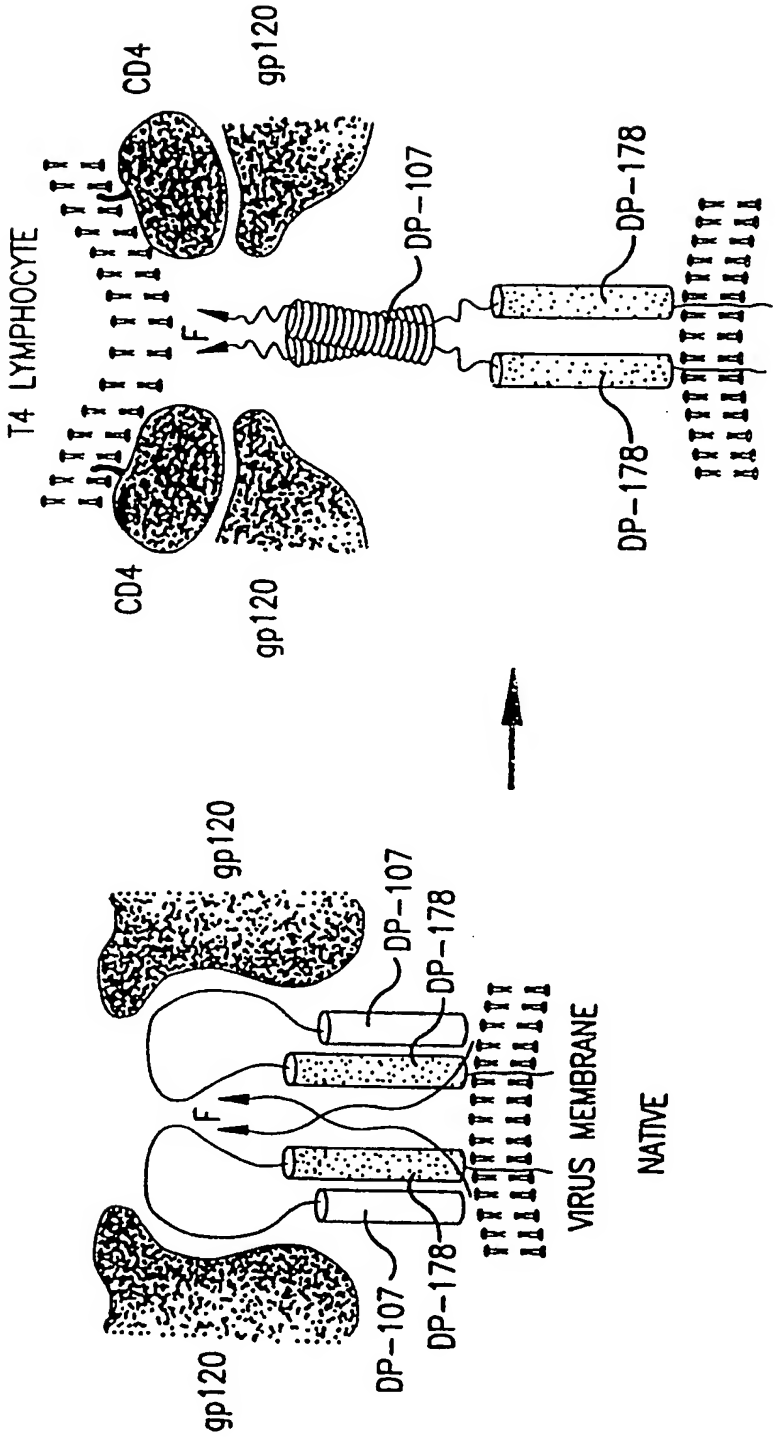


FIG.11A

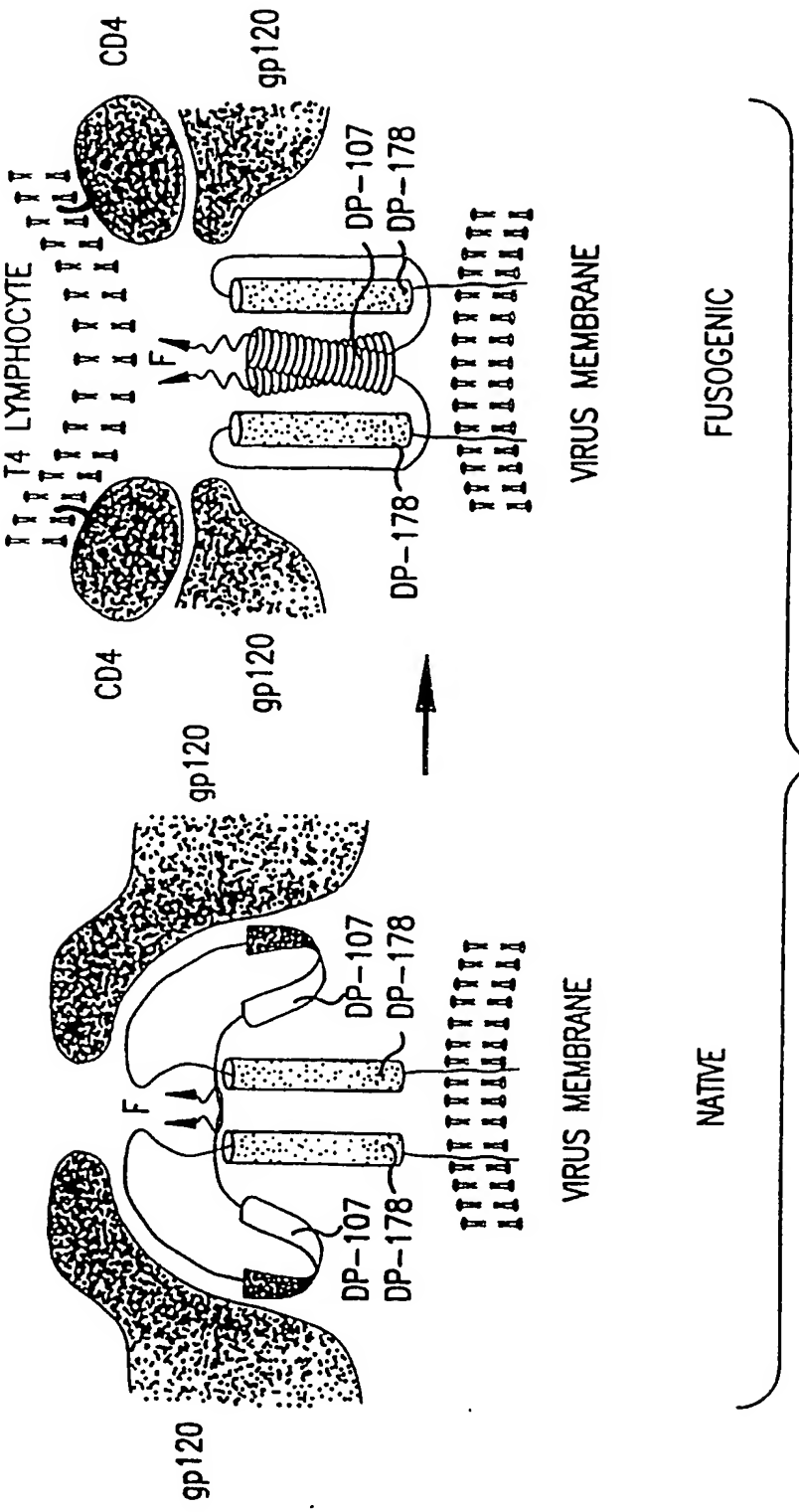


FIG.11B

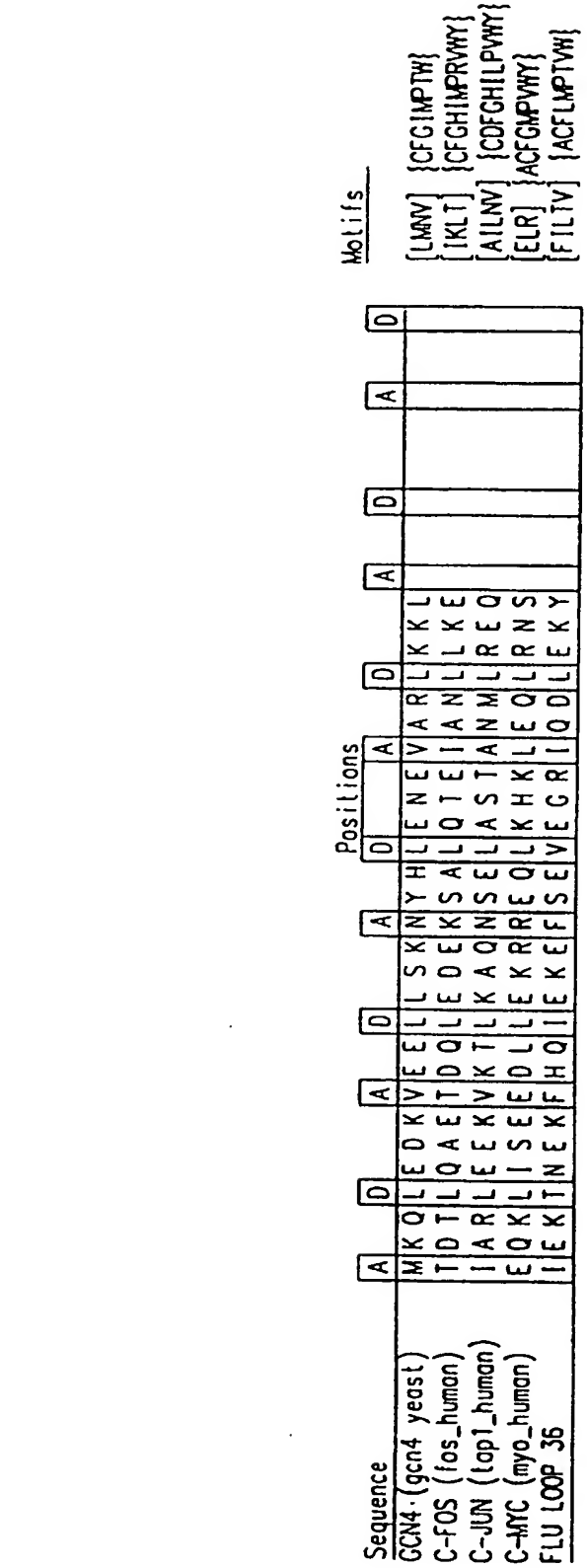


FIG.12

Positions

Sequence	A			D				A			D				A			D				A			D				A			D				A			D	Motifs
DP-107 (env_hv1bru)L1=D		N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I											[ILQT] {CFIMPSTY}
DP-107 (env_hv1bru)L1=D		N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L				[ILQTV] {CDFIMPST}
DP-107 (env_hv1bru)L1=D		N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L	K	D	Q	[ILQTV] {CDFIMPST}
DP-107 (env_hv1bru)L2=D	N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I												[EKLNQV] {CDFKMPSVY}
DP-107 (env_hv1bru)L2=D	N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L					[EKLNQV] {CFKMPS}
DP-107 (env_hv1bru)L2=D	N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L	K	D	Q		[EKLNQV] {CFKMPS}
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K												[EKLQY] {ACFGMPRVWY}
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W					[EKLQWY] {CFGMPRVY}
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F				[EFKLQWY] {CFGMPRVY}
DP-178 (env_hv1bru)Y1=D				Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K									[EILNQSY] {ACFGMPRVWY}
DP-178 (env_hv1bru)Y1=D				Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W		[EILNQSWY] {CFGMPRVY}
DP-178 (env_hv1bru)Y1=D				Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F	[EFILNQSWY] {CFGMPRVY}

FIG.13

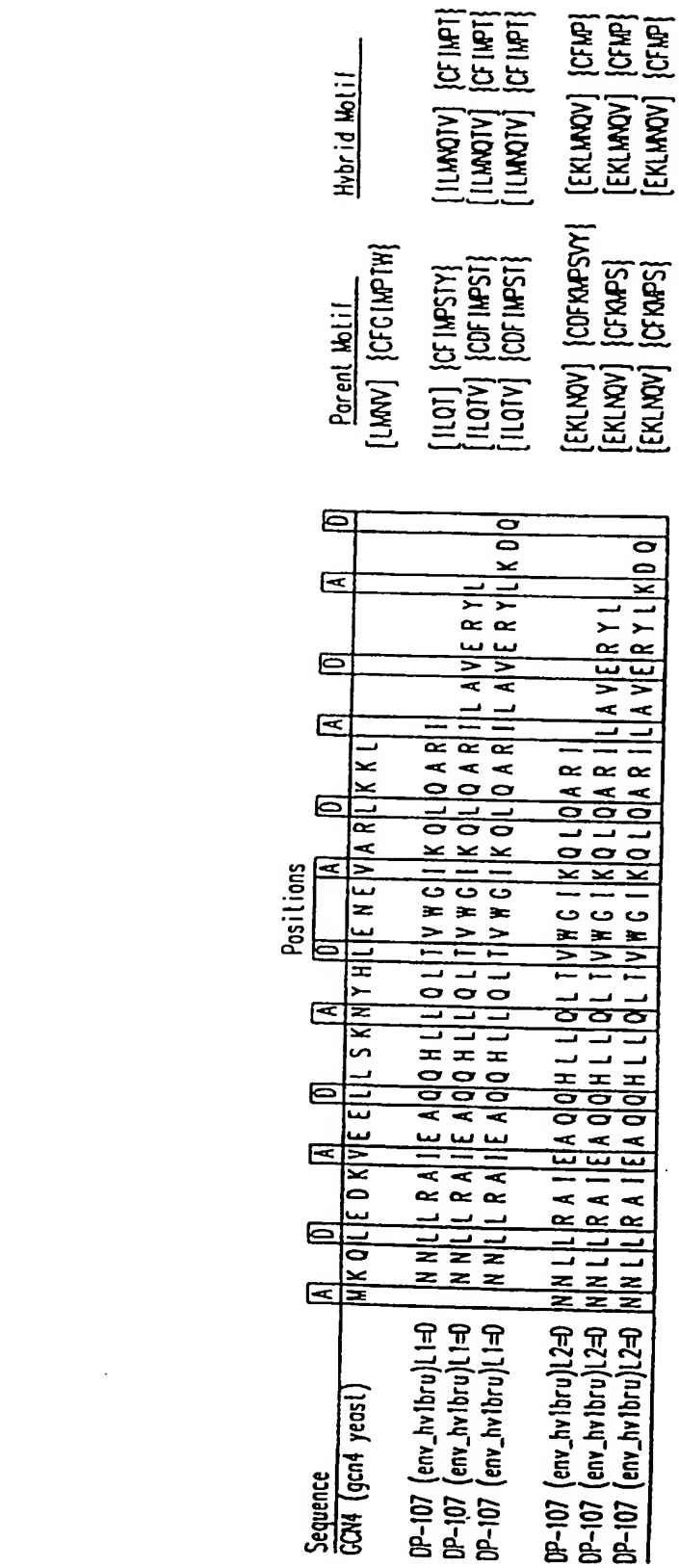


FIG. 14

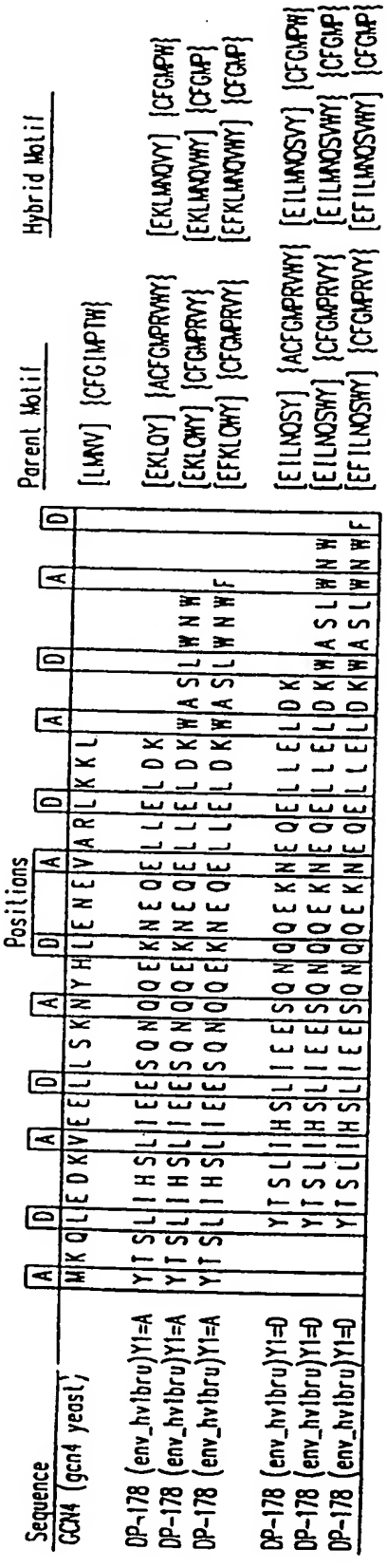


FIG. 15

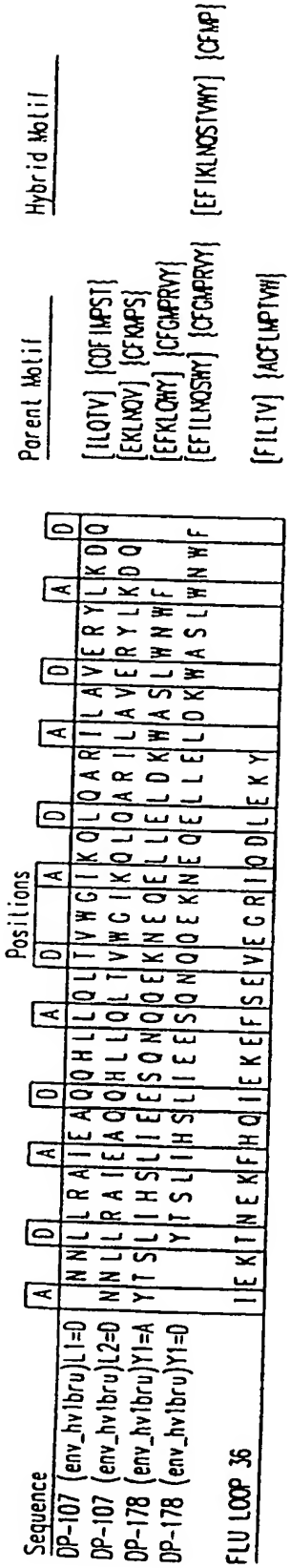


FIG.16

Sequence	Positions																																						Parent Motif	Hybrid Motif
	A		D			A		D			A		D			A		D			A		D			A		D			A		D					
GCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	E	L	L	S	K	N	Y	H	L	E	N	E	V	A	R	L	K	K	L										[LMNV]	[CFGIMPTW]	
DP-107 (env_hv1bru)L1=D		N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L	K	D	Q	[ILQTV]	[CDFIMPST]	
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	M	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F				[EFKLQWY]	[CFGMPRVY]	[EFIKLMNQTVWY]	[CFMP]
GCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	E	L	L	S	K	N	Y	H	L	E	N	E	V	A	R	L	K	K	L										[LMNV]	[CFGIMPTW]	
DP-107 (env_hv1bru)L1=D		N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L	K	D	Q	[ILQTV]	[CDFIMPST]	
DP-178 (env_hv1bru)Y1=D				Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F	[EFILNQSWY]	[CFGMPRVY]	[EFILMNQRSTVWY]	[CFMP]
GCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	E	L	L	S	K	N	Y	H	L	E	N	E	V	A	R	L	K	K	L										[LMNV]	[CFGIMPTW]	
DP-107 (env_hv1bru)L2=D	N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L	K	D	Q		[EKLNQV]	[CFKMPS]	
DP-178 (env_hv1bru)Y1=A	Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F				[EFKLQWY]	[CFGMPRVY]	[EFKLMNQVWY]	[CFMP]
GCN4 (gcn4 yeast)	M	K	Q	L	E	D	K	V	E	E	L	L	S	K	N	Y	H	L	E	N	E	V	A	R	L	K	K	L										[LMNV]	[CFGIMPTW]	
DP-107 (env_hv1bru)L2=D	N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L	K	D	Q		[EKLNQV]	[CFKMPS]	
DP-178 (env_hv1bru)Y1=D				Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F	[EFILNQSWY]	[CFGMPRVY]	[EFIKLMNQSVWY]	[CFMP]

FIG.17

Sequence	Positions																										Parent Motif	Hybrid Motif
	A		D		A		D		A		D		A		D		A		D		A		D		A			
GCN4 (gcn4_yeast)	M	K	Q	L	E	D	K	V	E	E	L	L	S	K	N	Y	H	L	E	N	E	V	A	R	L	K	K	L		
DP-107 (env_hv1bru)L1=D		N	N	L	L	R	A	I	T	E	A	Q	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L	K	D	Q	[LMNV] {CFGIMPTW}
DP-107 (env_hv1bru)L2=D		N	N	L	L	R	A	I	E	A	Q	Q	H	L	L	Q	L	T	V	W	G	I	K	Q	L	Q	A	R	I	L	A	V	E	R	Y	L	K	D	Q	[ILQTV] {CDFIMPST}
DP-178 (env_hv1bru)Y1=A		Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F				[EKLNQV] {CFKMPS}
DP-178 (env_hv1bru)Y1=D			Y	T	S	L	I	H	S	L	I	E	E	S	Q	N	Q	Q	E	K	N	E	Q	E	L	L	E	L	D	K	W	A	S	L	W	N	W	F				[EFKLQWY] {CFGMPRVY}
C-FOS (fos_human)		T	D	T	L	Q	A	E	T	D	Q	L	E	D	E	K	S	A	L	Q	T	E	I	I	A	N	L	L	K	E												[EFILNQSWY] {CFGMPRVY}
C-JUN (tap1_human)		I	A	R	L	E	E	K	V	K	T	L	K	A	Q	N	S	E	L	A	S	T	A	N	W	L	R	E	Q													[IKLT] {CFGHIMPRWY}
C-MYC (myc_human)		E	Q	K	L	I	S	E	E	D	L	L	R	K	R	R	E	Q	L	K	H	K	L	E	Q	L	R	N	S													[AILNV] {CDFGHILPWY}
FLU LOOP 36		I	I	E	K	T	N	E	K	F	H	Q	I	E	K	S	L	E	E	I	E	G	R	I	Q	D	L	E	K	Y													[ELR] {ACFGMPWY}
																																										[FILTV] {ACFLMPTWY}
																																											= {CDGHP} {CFP}

FIG. 18

P-[LIV]-{P}(6)-[LIV]-{P}(6)-[LIV]
P-{P}(1)-[LIV]-{P}(6)-[LIV]-{P}(6)-[LIV]
P-P}(2)-[LIV]-P}(6)-[LIV]-P}(6)-[LIV]
P-P}(3)-[LIV]-P}(6)-[LIV]-P}(6)-[LIV]
P-P}(4)-[LIV]-P}(6)-[LIV]-P}(6)-[LIV]
P-P}(5)-[LIV]-P}(6)-[LIV]-P}(6)-[LIV]
P-P}(6)-[LIV]-P}(6)-[LIV]-P}(6)-[LIV]
P-P}(7)-[LIV]-P}(6)-[LIV]-P}(6)-[LIV]
P-P}(8)-[LIV]-P}(6)-[LIV]-P}(6)-[LIV]
P-P}(9)-[LIV]-P}(6)-[LIV]-P}(6)-[LIV]
P-P}(10)-[LIV]-P}(6)-[LIV]-P}(6)-[LIV]
P-X(1,12)-[LIV]-P}(6)-[LIV]-P}(6)-[LIV]
P-X(13,23)-[LIV]-P}(6)-[LIV]-P}(6)-[LIV]

FIG.19

Fusion Peptide ▼ALLMOTI5▼

▼.....ILGELG A AGSTMGARSM TLTVQARQ ▲107x178x4▲ ▲LL SGIVQQQ *DP107-NNL*

LRAIEAQQHL LQLTVWGIKQ LQARILAVER YLKDQ-DP107 QLLG▲▼ I WGC

▼ALLMOTI5▼ ▲107x178x4▲

SGKLICT TAVP ▼WNASWS NKSLEQIWNN MTWM ♦E ▲WDREINN *DP178-*

YTSLIHSL IEESQNQQEK NEQELLELDK♦ WASLWNWF-DP178 NI

♦Transmembrane Region♦

TNWLWYIK▲ ♦IF IMIVGGLVGL RIVFAVLSIV NRVRQGYS▼ PL

✣P23LZIPC✣

SFQTHLPTPR GPDR ✣PEGIEE EGGERDRDRS IRLVNGSLAL IWDDLRSL✣ CL

▼ALLMOTI5▼ ▲107x178x4▲

F ▼SYHRLRDLL LIVTRIVELL GRRGW ▲EALKY WWNLLQYWSQ

ELKNSAVSLL NAT▲ AIAVAEG TDRVIEVVQG A▼ CRAIRHIPR

RIRQGLERIL L

FIG. 20

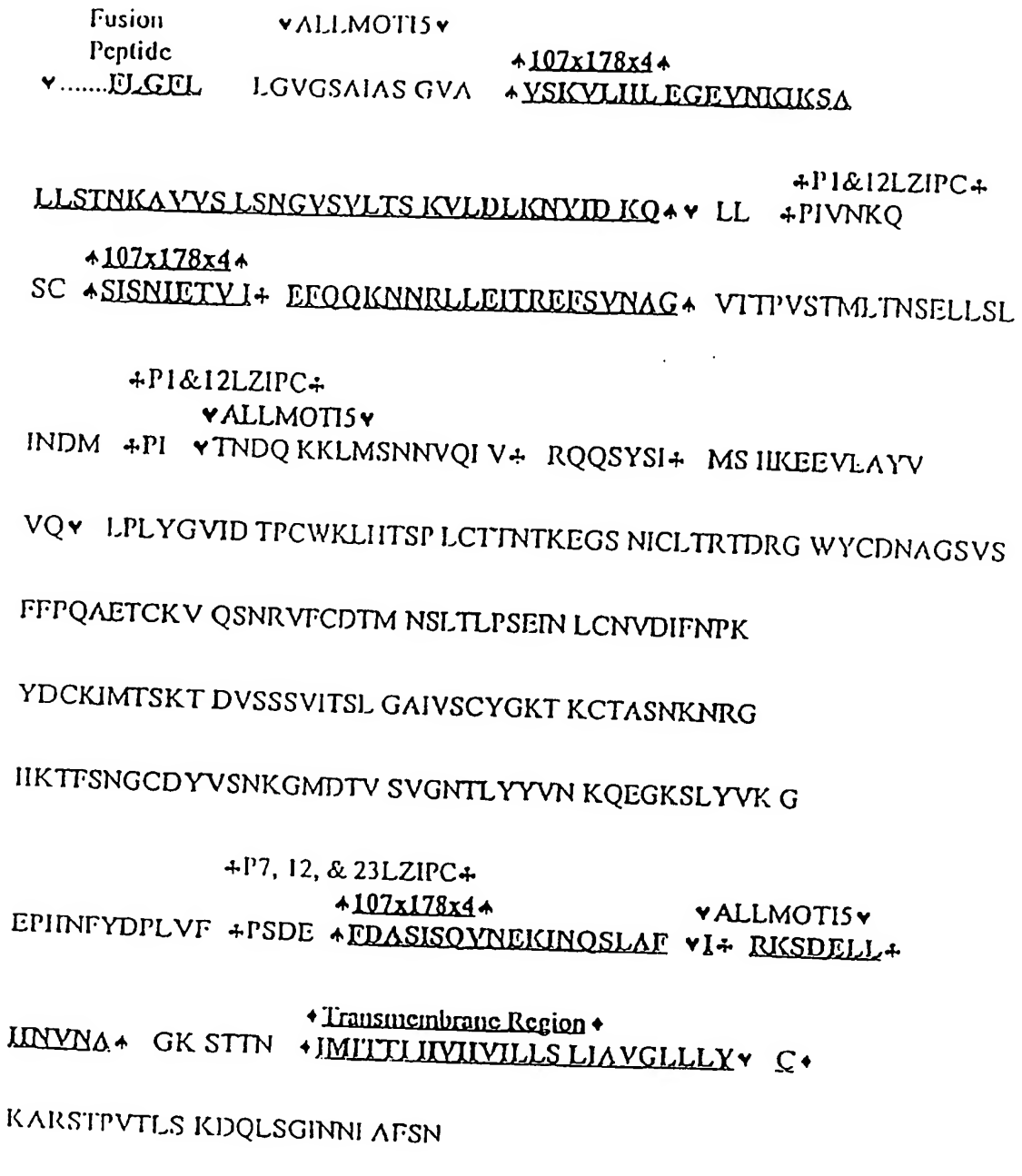


FIG. 21

Fusion
Peptide ▼ALLMOTI5▼ ▲107x178x4▲
.....ELGELG ▼AAGTA MGAAA ▲TALTVQSQHLLAGILQQQKNLLAAV

▲107x178x4▲
EAQ▲ QQM ▲LKLTIWGVKNLNARYTALEKYLEDQARLN▲ AWG▼ CA

♦LVS Coiled-Coil♦
▼ALLMOTI5▼ ▲107x178x4▲
WKQVCHTTVP WQWNNRTPDW ▼NNMT ♦WLE ▲WERQISYLEGNIT

▲107x178x4▲
TQLEEARAQEEKNLD▲ AYQKLSS♦ WSDFWSW▼ FDF ▲SKWLN ♦ILK

♦Transmembrane Region♦
IGELDVLGIIGLRLLYTV♦ YS▲ CIARVRQGYS PLSPQHHHP WKGQPDNAEG

PGEGGDKRKN SSEPWQKESG TAEWKSNWCK RLTNWCSISS IWLYNS

▼ALLMOTI5▼
▼CLTL LVHLRSAFQY IQYGLGELKA AAQEAVVALA RLAQNAGYQIWL▼

ACRSAYRA IINSPRRVRQ GLEGILN

FIG. 22

Fusion ♦107x178x4♦
Peptide ♥ALLMOTI5♥ ♦LVS Coiled-Coil♦
.....EAG ♥VVL AGVALGVATA AQITAGIALHQ ♦♦SNLNAQAIQ

SLRTSLEQSNKAIEEIREATQETVIA♦ VQGVQDY♦ VNNEL♥ VP

♥ALLMOTI5♥
♦107x178x4♦
♣P6 & 12LZIPC♣
AMQHMSCELVGQRLGLRLLRYYTELLSIFGPSLRD ♣PISA ♦♥EISIQALIYAL

GGELIIKILEKLGYSGSD♦ MIAILESRGIKTKI♥ TIIVDLPGKF IILSISY

♣P1 & 12LZIPC♣
♣PTLSEVKGVIVHRLEAV♣ SYNIGSQEWYTTVPRYIATNGYLISNFDESSCVFVS

ESAICSQNSL YPMSPLLQQC IRGDTSSCAR TLVSGTMGNK FILSKGNIVA

NCASILCKCY STSTIINQSP DKLLTFIASD TCPLVEIDGA TIQVGGRQYP

♦LVS Coiled-Coil♦
♥ALLMOTI5♥
♣P12 & 23LZIPC♣
DMVYEGKVAL G ♣PAISLD ♥RL♦DVGTNLGNALKKLDDAKVLI♣

♦Transmembrane Region♦
DSS♣ NQILETVR RS♥♦ SFN ♦FGSLL SVPILSCIAL ALLLLIYCC♦

K RRYQQTLKQH TKVDPAFKPD LTGTSKSYVR SL

FIG. 23

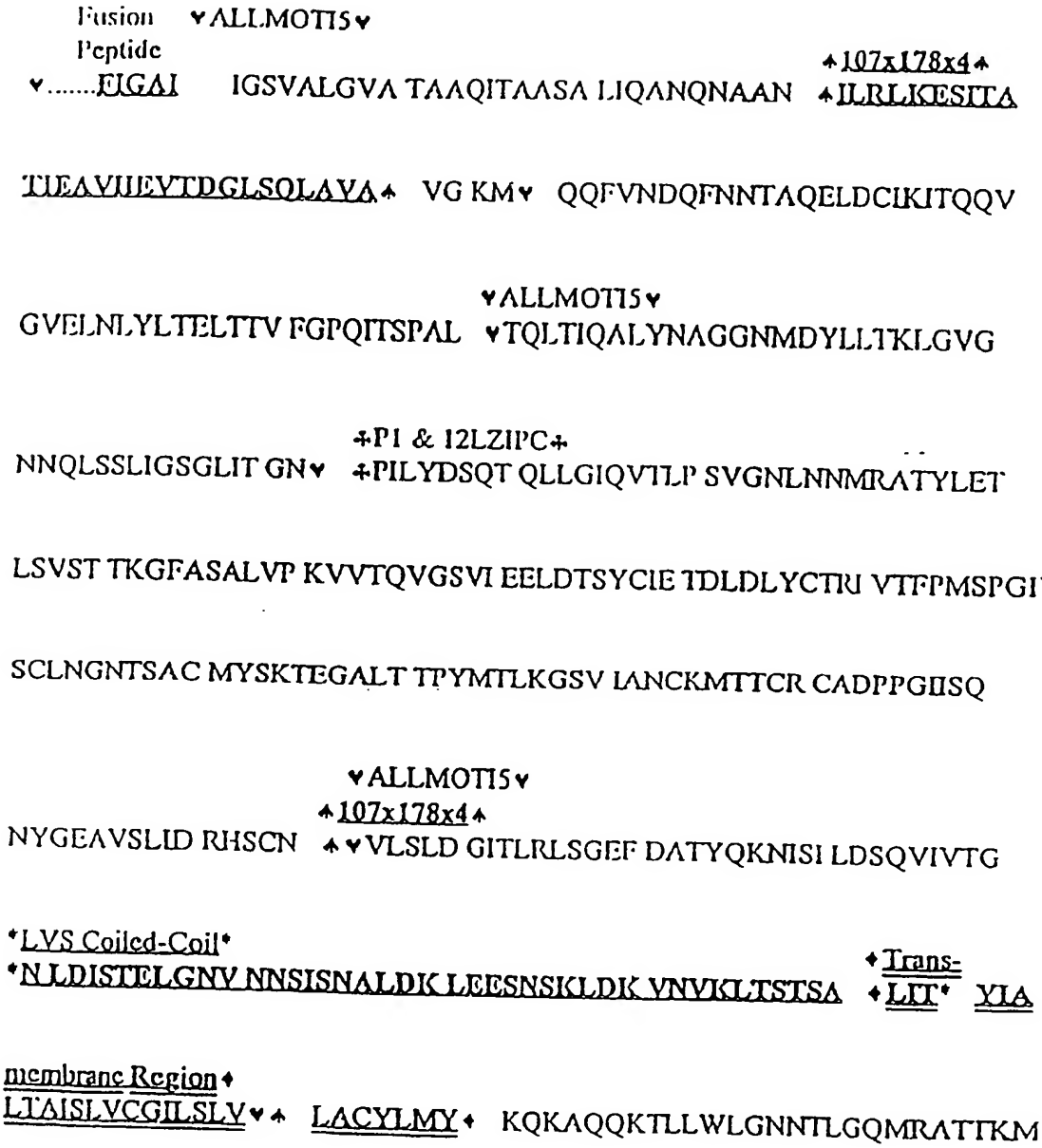


FIG. 24

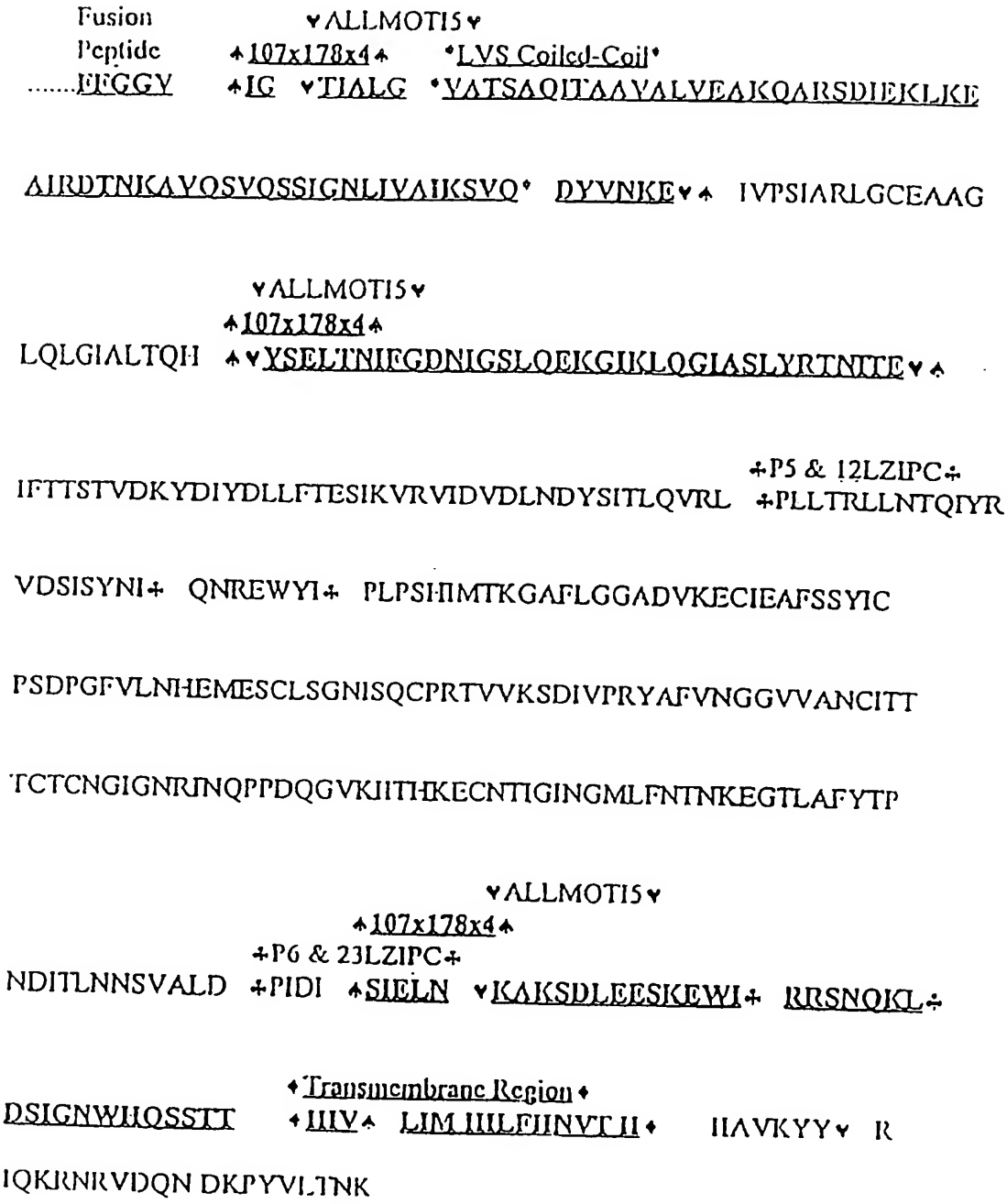


FIG. 25

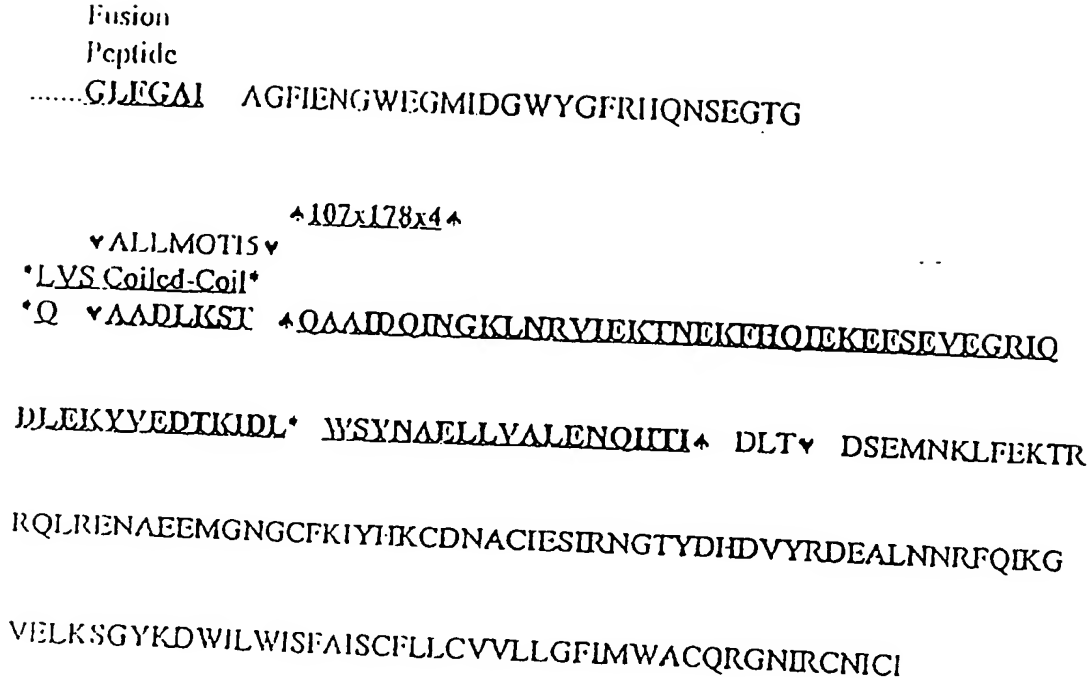


FIG. 26

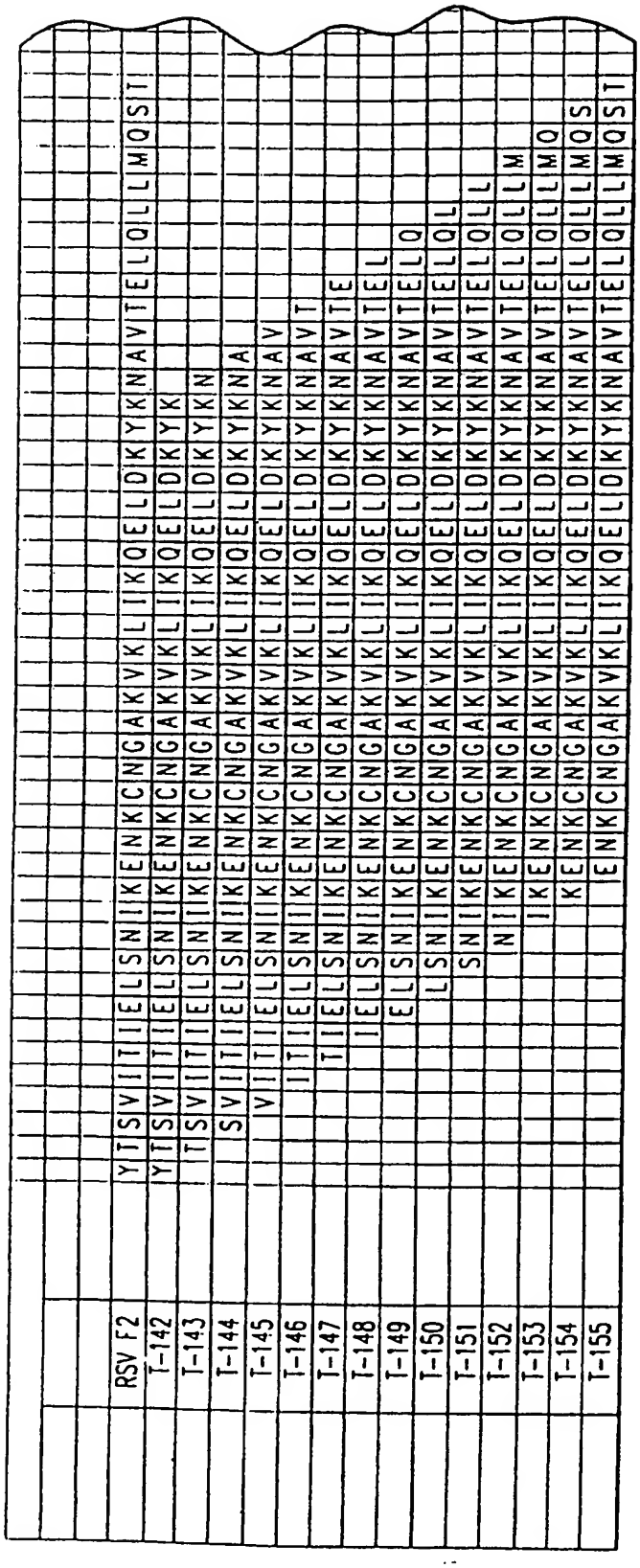
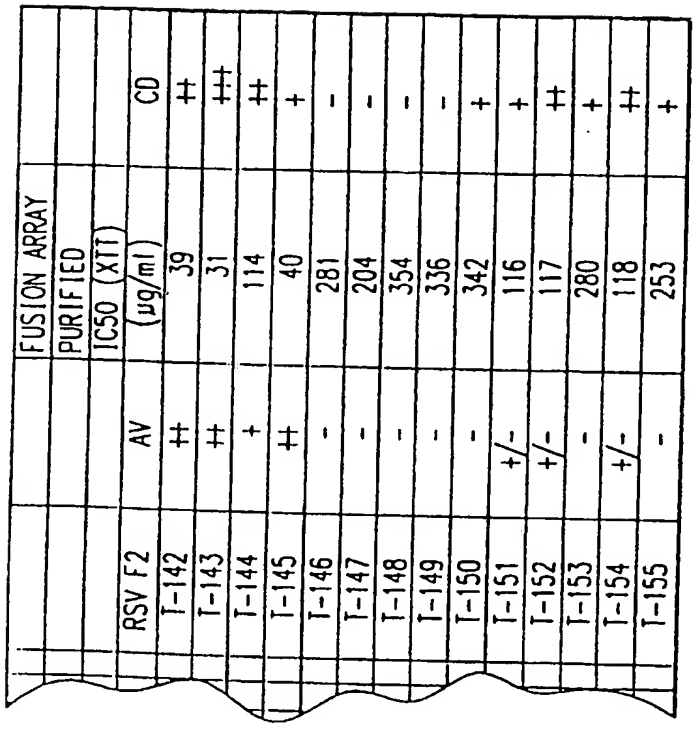


FIG.27A



	FUSION ARRAY	
	PURIFIED	
	IC50 (XTT)	
RSV F2	AV	CD
	(μg/ml)	
T-142	++	39	++
T-143	++	31	+++
T-144	+	114	++
T-145	++	40	+
T-146	-	281	-
T-147	-	204	-
T-148	-	354	-
T-149	-	336	-
T-150	-	342	+
T-151	+/-	116	+
T-152	+/-	117	++
T-153	-	280	+
T-154	+/-	118	++
T-155	-	253	+

FIG.27B

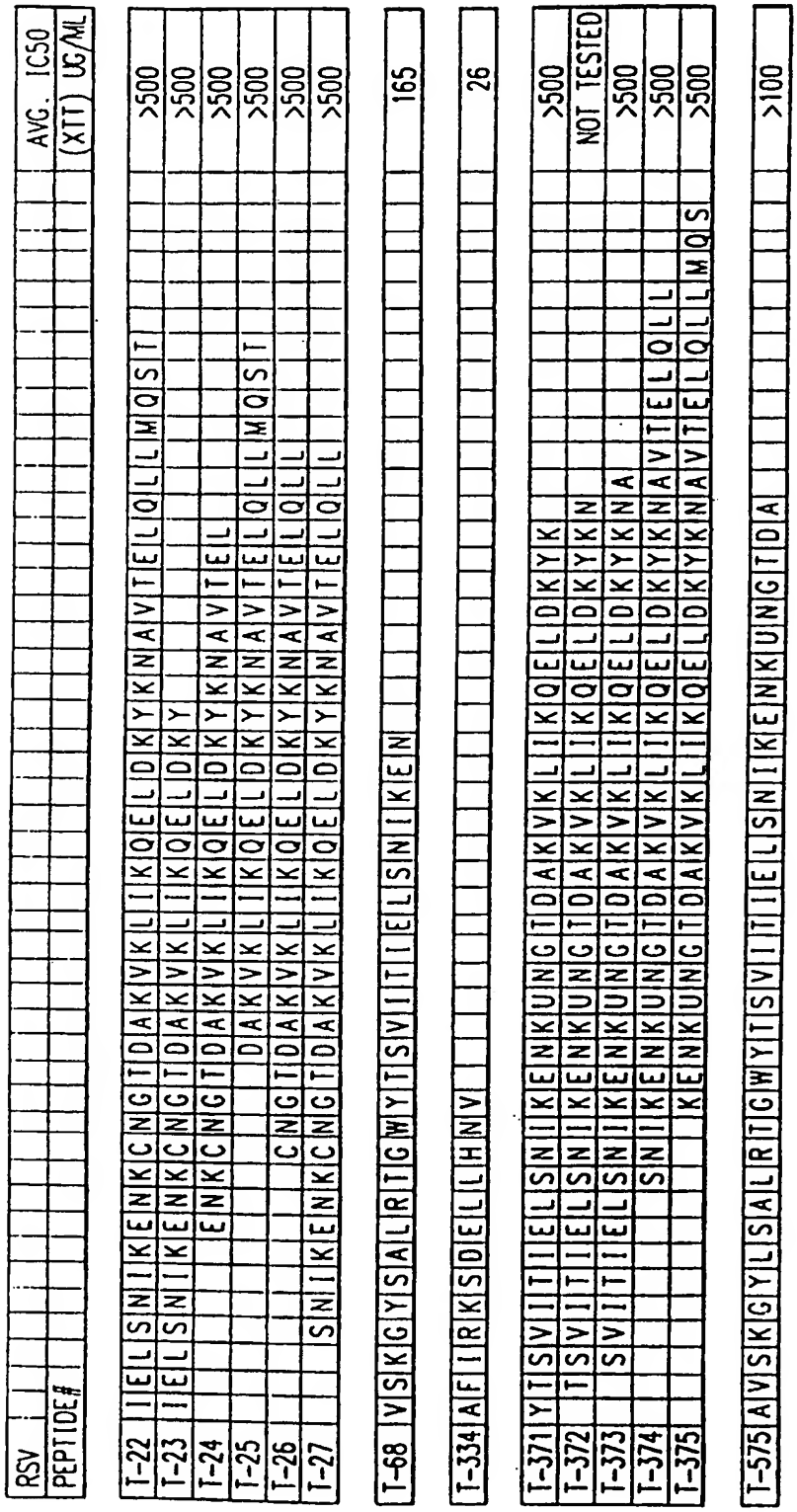


FIG.27C

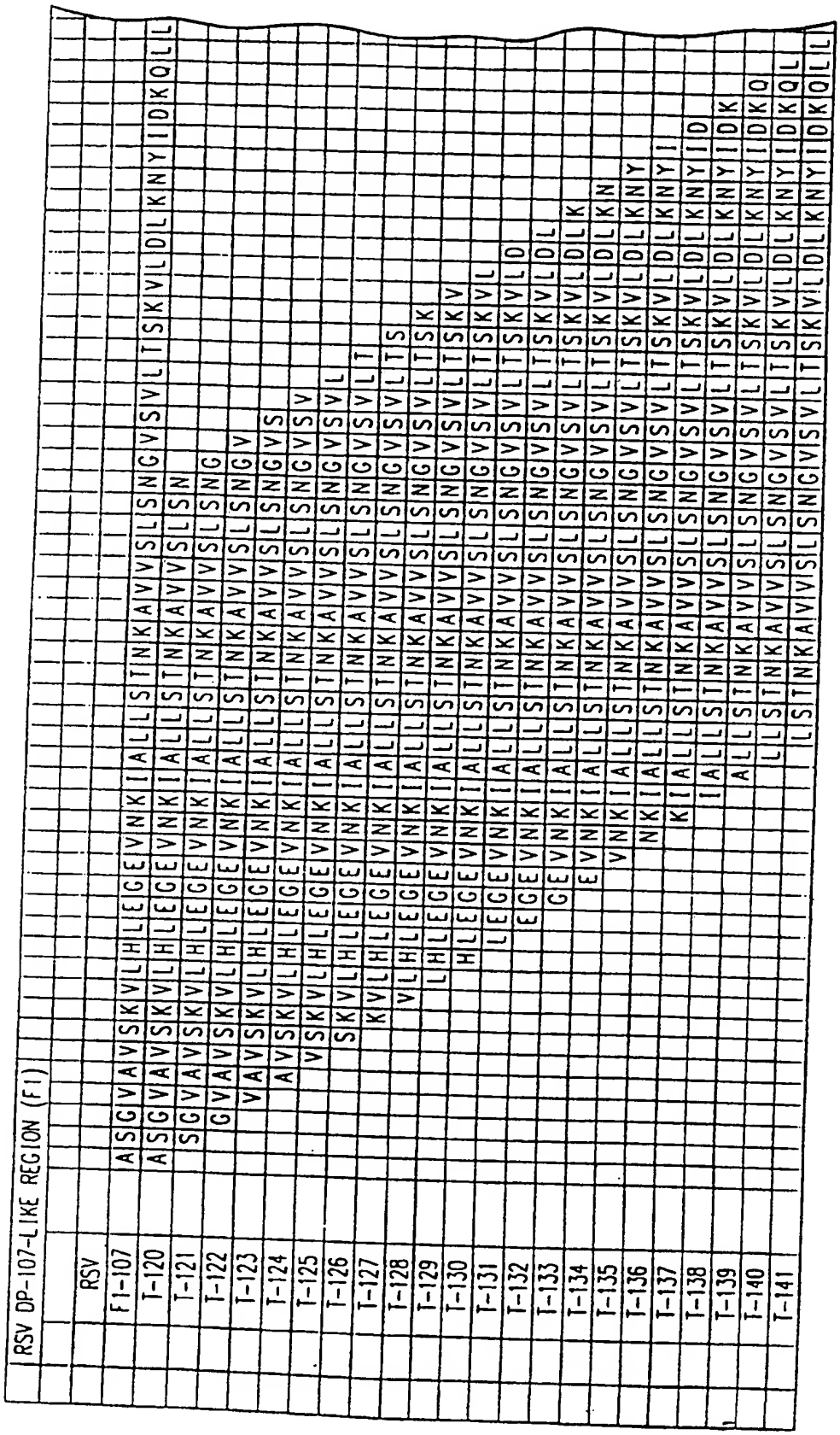


FIG.27D

		FUSION ASSAY	
		PURIFIED	
RSV		IC50 XTT	
F-107	AV	(µg/ml)	CO
T-120	-	204	-
T-121	-	354	-
T-122	-	347	-
T-123	+/-	126	-
T-124	+	95	-
T-125	+	84	-
T-126	+	89	-
T-127	+	89	-
T-128	-	206	-
T-129	-	343	-
T-130	-	177	-
T-131	+/-	118	-
T-132	-	272	-
T-133	+/-	307	-
T-134	+/-	187	-
T-135	+	60	-
T-136	-	194	-
T-137	+	99	-
T-138	++	38	-
T-139	+	86	+/-
T-140	-	160	+/-
T-141	-	204	+/-

FIG.27E

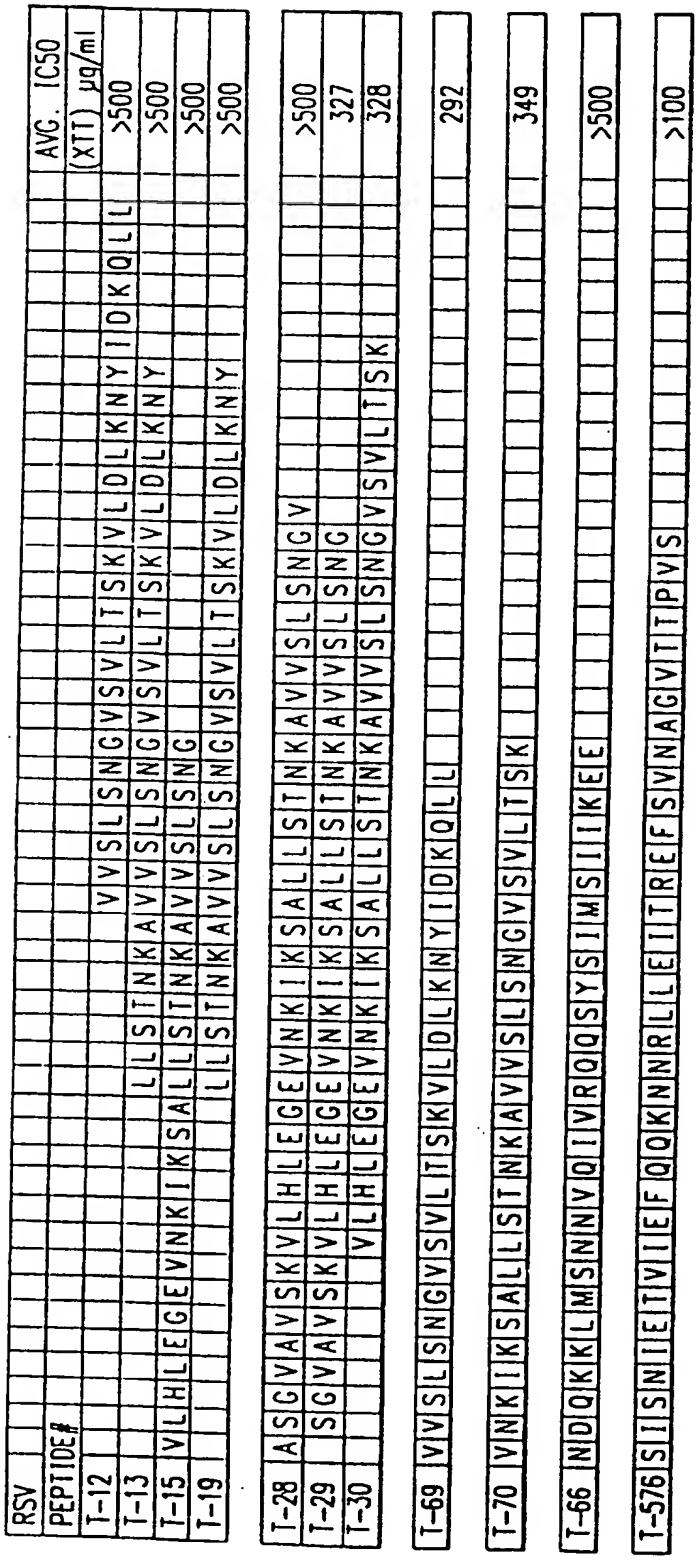


FIG.27F

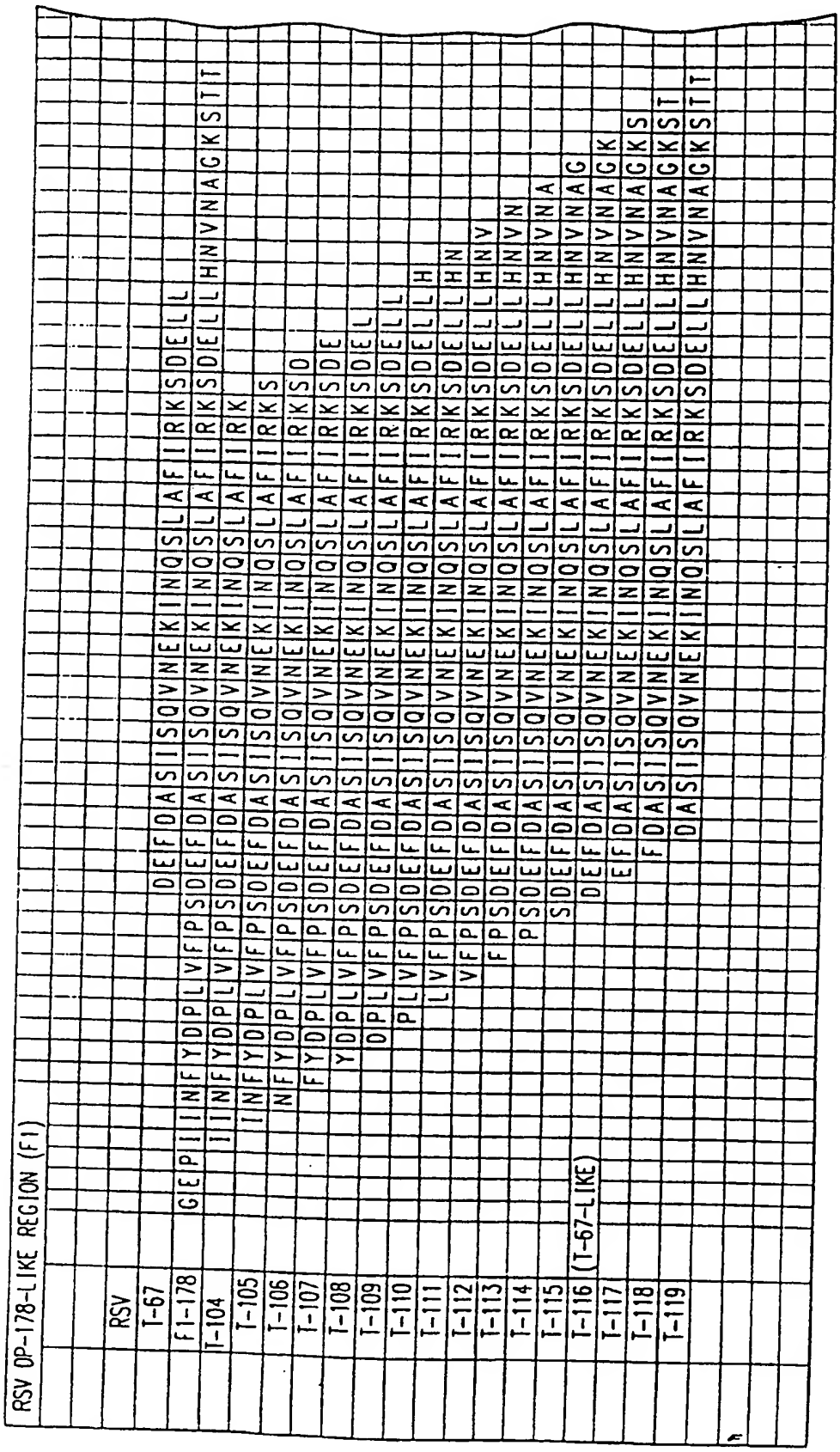
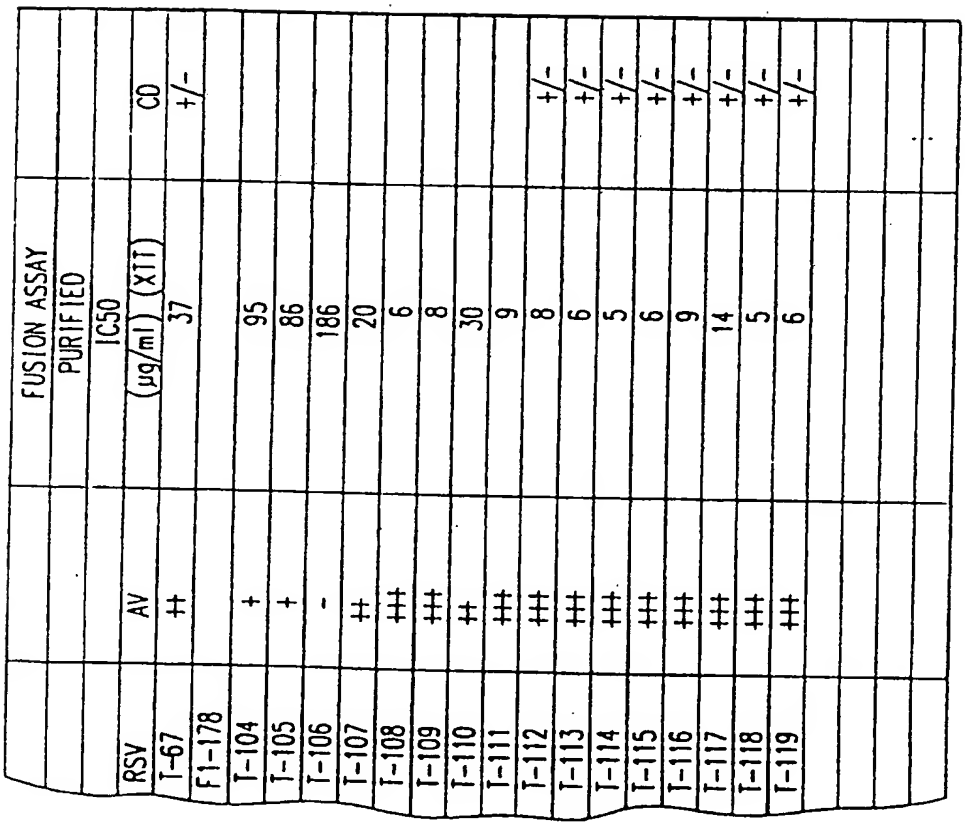
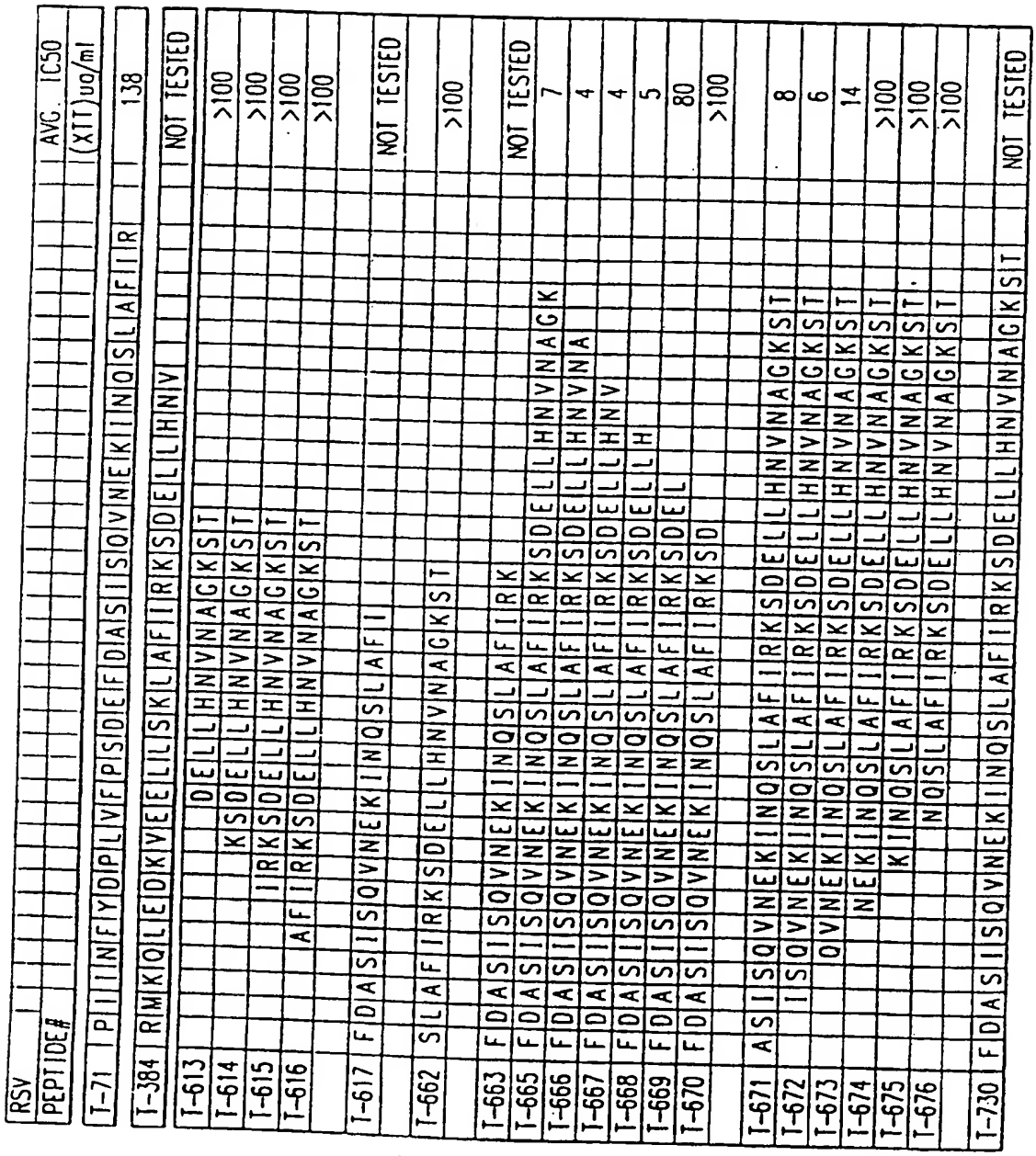


FIG.28A



		FUSION ASSAY	
		PURIFIED	
		IC50	
RSV	AV	(µg/ml) (XTT)	CD
T-67	++	37	+/-
F1-178			
T-104	+	95	
T-105	+	86	
T-106	-	186	
T-107	++	20	
T-108	++	6	
T-109	++	8	
T-110	++	30	
T-111	++	9	
T-112	++	8	+/-
T-113	++	6	+/-
T-114	++	5	+/-
T-115	++	6	+/-
T-116	++	9	+/-
T-117	++	14	+/-
T-118	++	5	+/-
T-119	++	6	+/-

FIG.28B



RSV PEPTIDE#	AVG. IC50 (XTT) ug/ml
T-71 PIIINFYDIPLVFPISDEFDASIISQVNEKIINQSLAFIIR	138
T-384 RIMKQLEDKVEELILSKLAFIIRKSDELLHNV	NOT TESTED
T-613 DELLHNVNAGKST	>100
T-614 KSDELLHNVNAGKST	>100
T-615 IIRKSDELLHNVNAGKST	>100
T-616 AFIIRKSDELLHNVNAGKST	>100
T-617 FDASIISQVNEKIINQSLAFII	NOT TESTED
T-662 SLAFIIRKSDELLHNVNAGKST	>100
T-663 FDASIISQVNEKIINQSLAFIIRK	NOT TESTED
T-665 FDASIISQVNEKIINQSLAFIIRKSDELLHNVNAGK	7
T-666 FDASIISQVNEKIINQSLAFIIRKSDELLHNVNA	4
T-667 FDASIISQVNEKIINQSLAFIIRKSDELLHNV	4
T-668 FDASIISQVNEKIINQSLAFIIRKSDELLH	5
T-669 FDASIISQVNEKIINQSLAFIIRKSDEL	80
T-670 FDASIISQVNEKIINQSLAFIIRKSD	>100
T-671 ASIISQVNEKIINQSLAFIIRKSDELLHNVNAGKST	8
T-672 IISQVNEKIINQSLAFIIRKSDELLHNVNAGKST	6
T-673 QVNEKIINQSLAFIIRKSDELLHNVNAGKST	14
T-674 NEKIINQSLAFIIRKSDELLHNVNAGKST	>100
T-675 KIINQSLAFIIRKSDELLHNVNAGKST	>100
T-676 NQSLAFIIRKSDELLHNVNAGKST	>100
T-730 FDASIISQVNEKIINQSLAFIIRKSDELLHNVNAGKSIT	NOT TESTED

FIG.28C

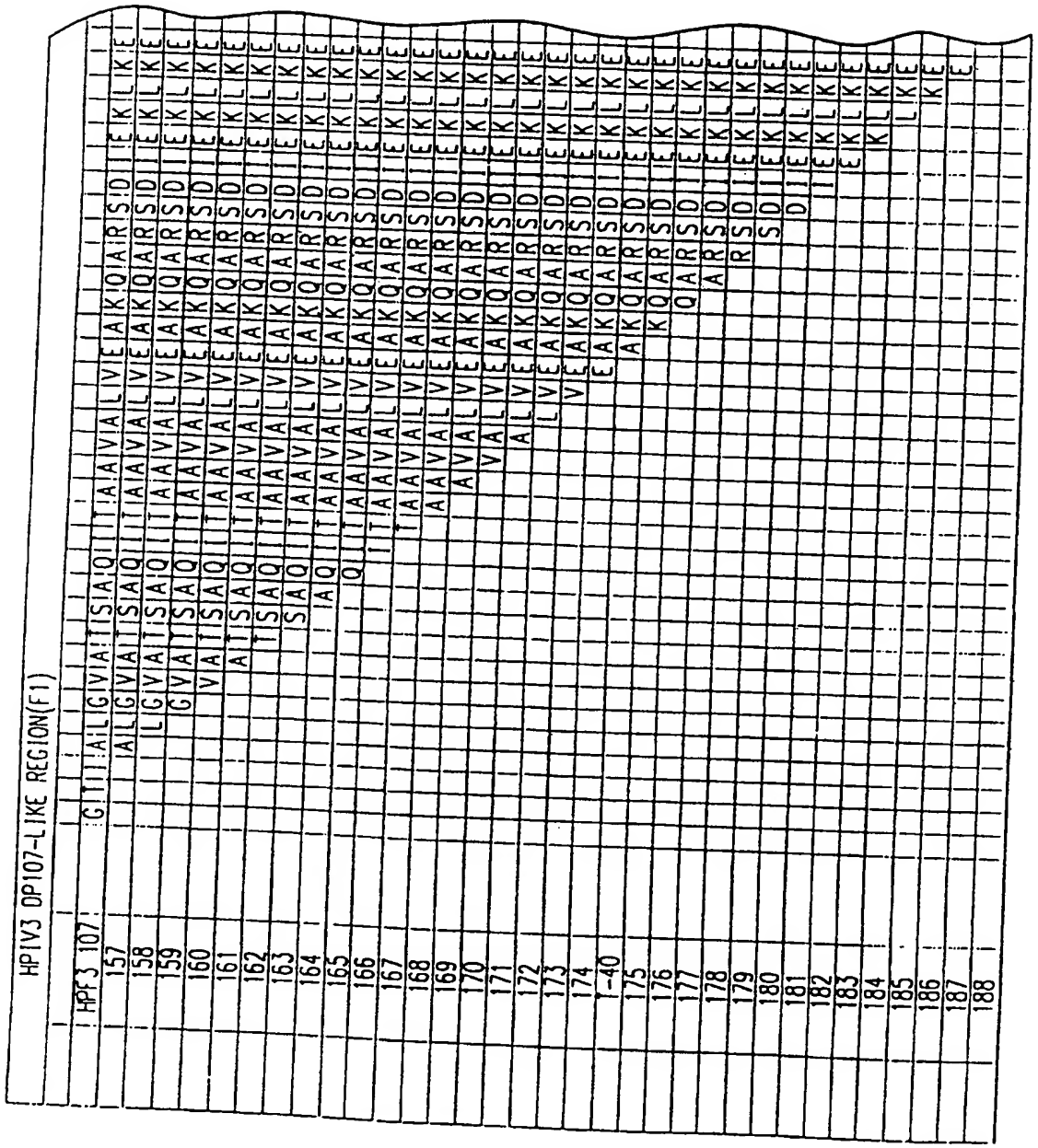


FIG.29A

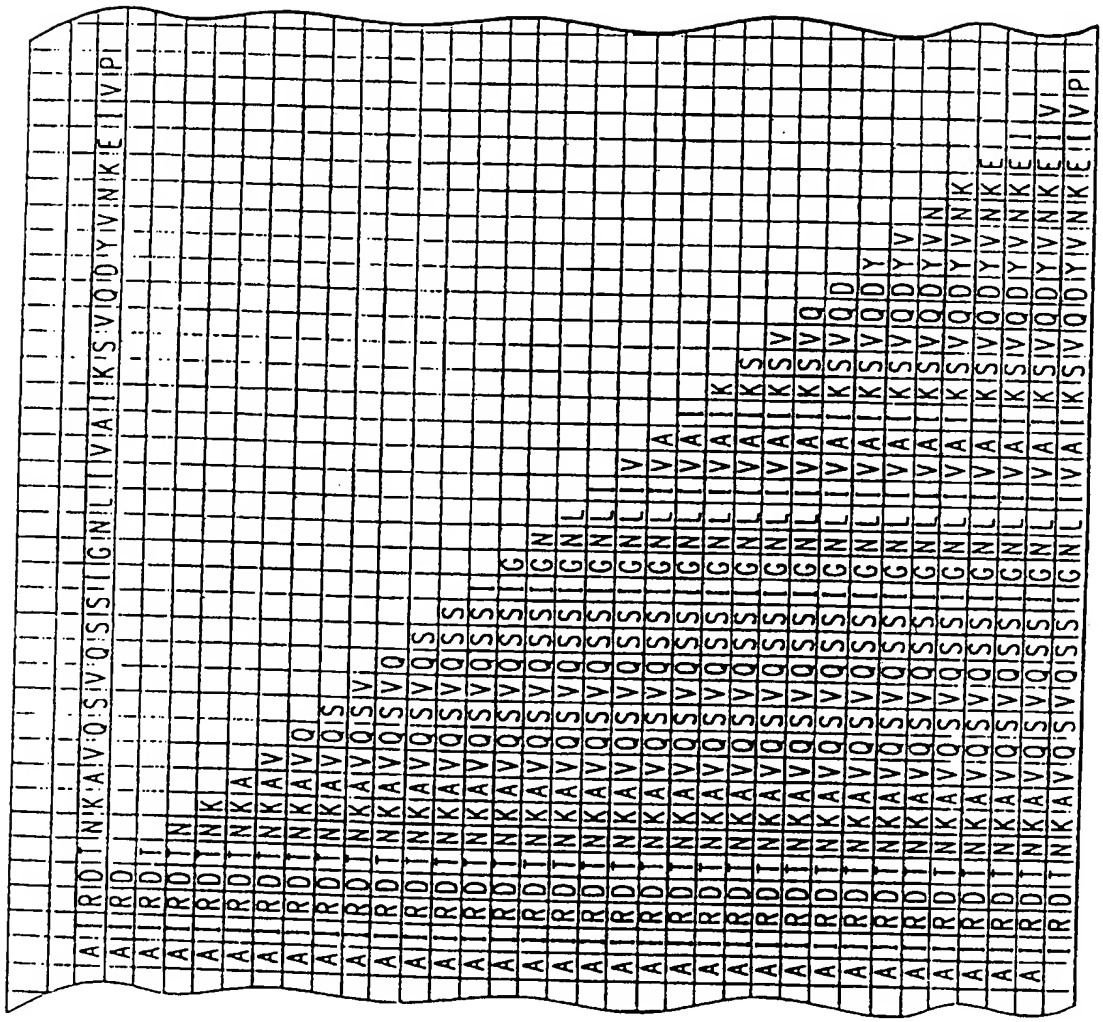
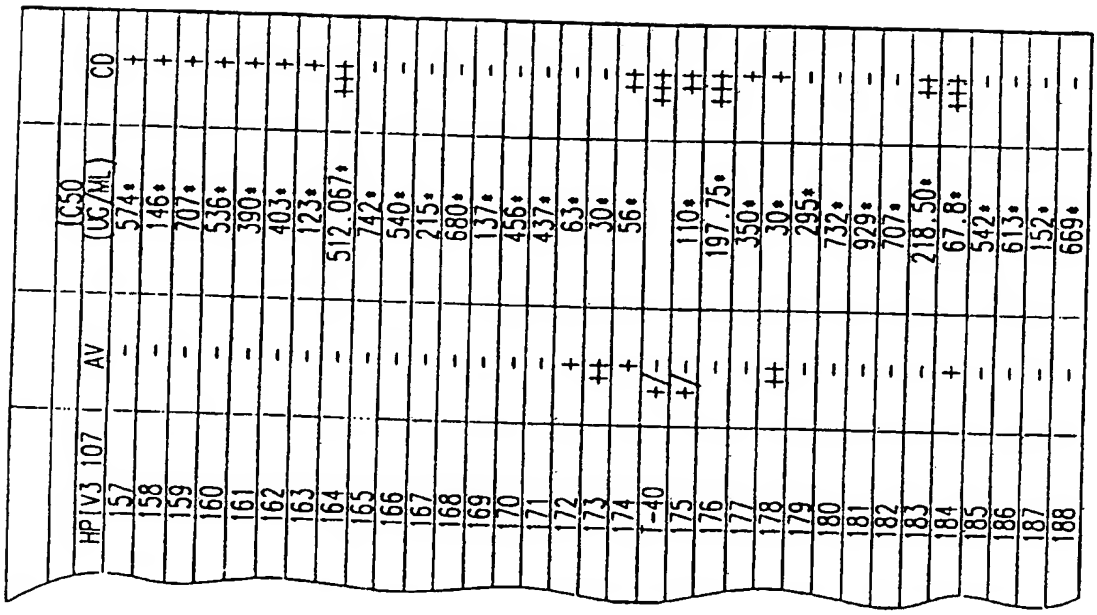


FIG.29B



HPIV3 107	AV	IC50 (UG/ML)	CO
157	-	574*	+
158	-	146*	+
159	-	707*	+
160	-	536*	+
161	-	390*	+
162	-	403*	+
163	-	123*	+
164	-	512.067*	++
165	-	742*	-
166	-	540*	-
167	-	215*	-
168	-	680*	-
169	-	137*	-
170	-	456*	-
171	-	437*	-
172	+	63*	-
173	++	30*	-
174	+	56*	++
T-40	+/-		++
175	+/-	110*	++
176	-	197.75*	++
177	-	350*	+
178	++	30*	+
179	-	295*	-
180	-	732*	-
181	-	929*	-
182	-	707*	-
183	-	218.50*	++
184	+	67.8*	++
185	-	542*	-
186	-	613*	-
187	-	152*	-
188	-	669*	-

FIG.29C

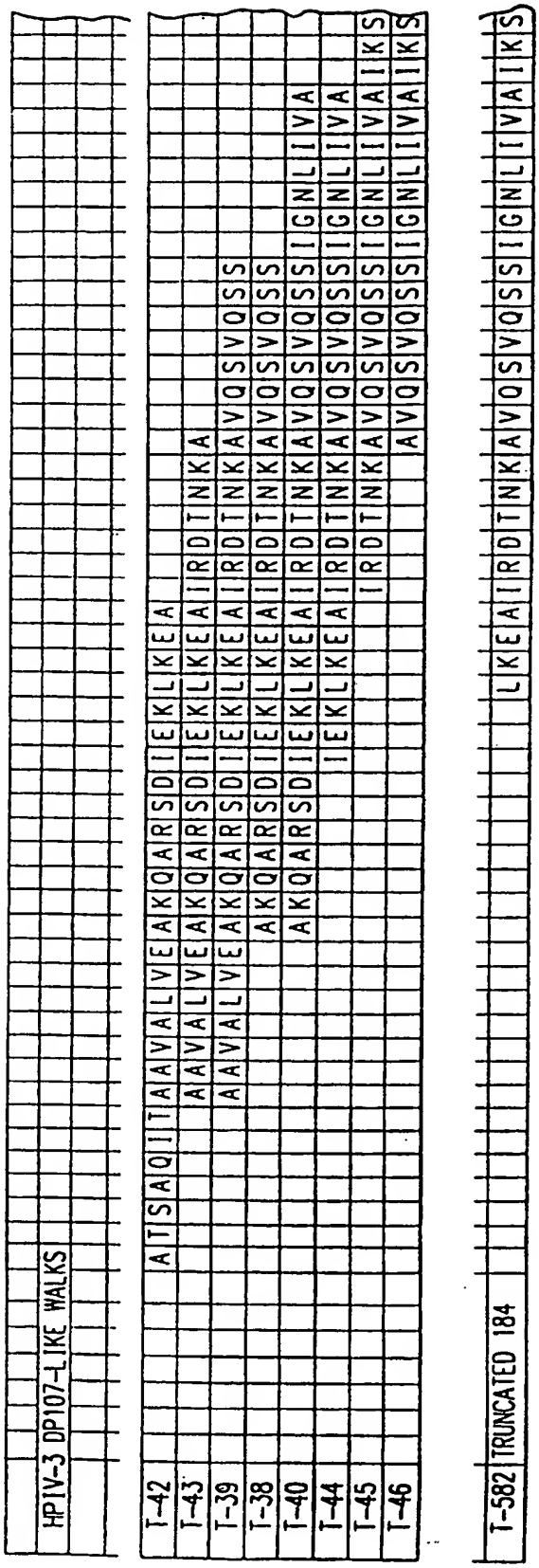


FIG.29D

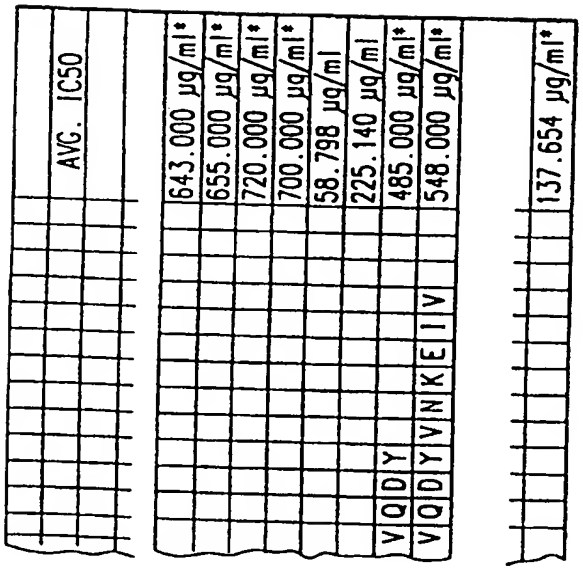


FIG.29E

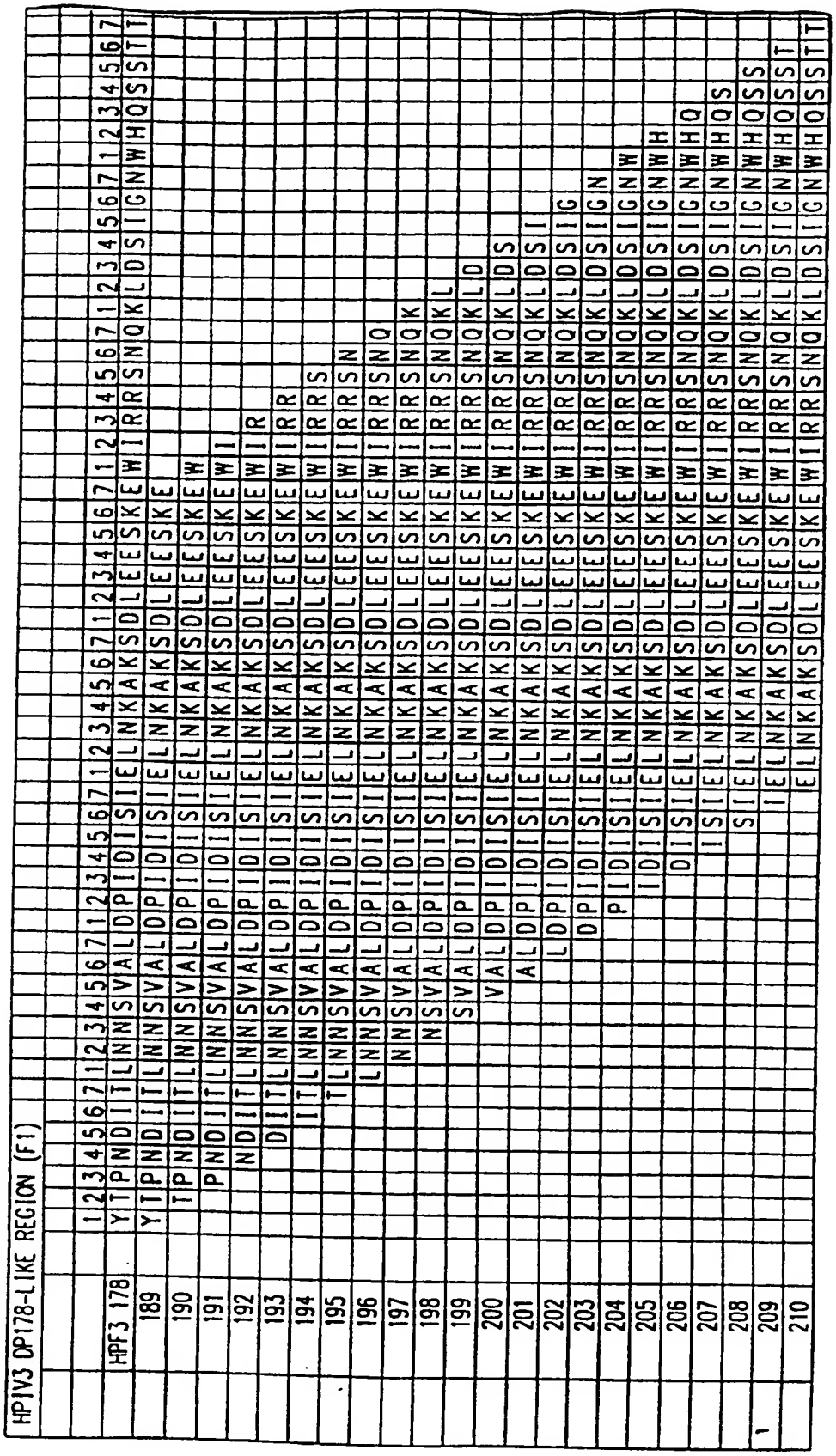
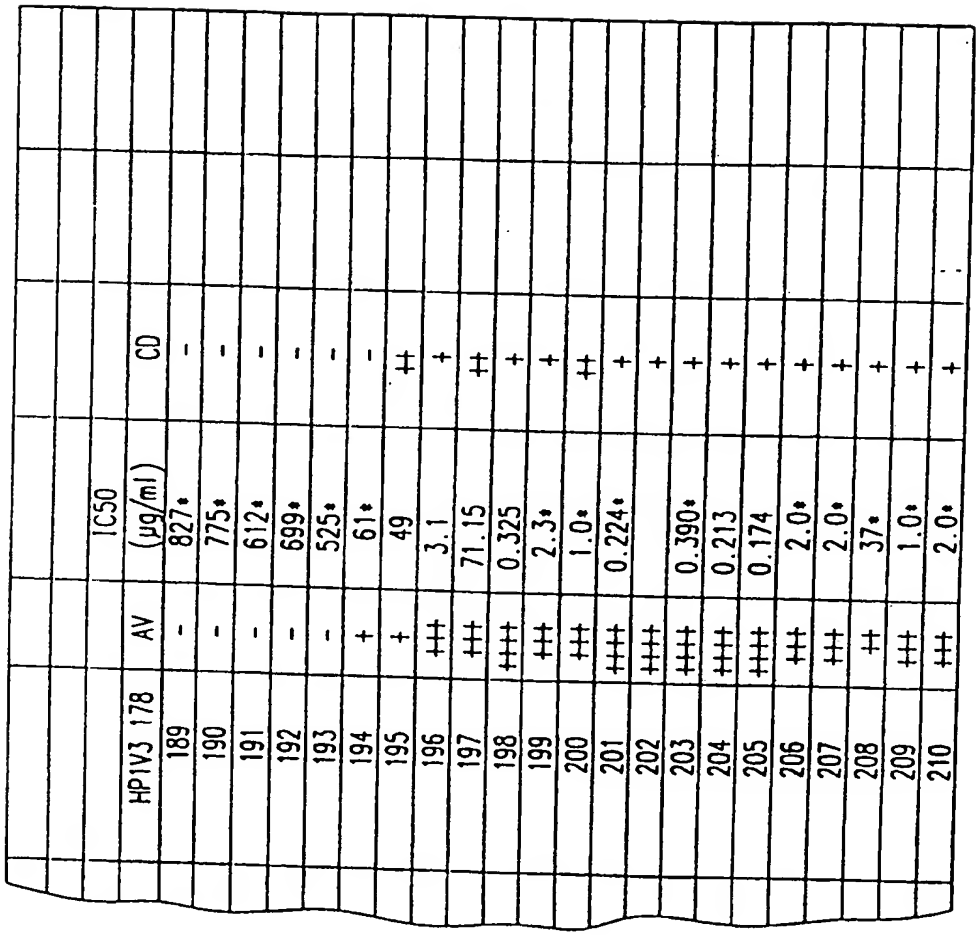


FIG.30A



HP1V3 178	AV	IC50 (μg/ml)	CD
189	-	827*	-
190	-	775*	-
191	-	612*	-
192	-	699*	-
193	-	525*	-
194	+	61*	-
195	+	49	++
196	+++	3.1	+
197	++	71.15	++
198	+++	0.325	+
199	++	2.3*	+
200	++	1.0*	++
201	+++	0.224*	+
202	+++		+
203	+++	0.390*	+
204	+++	0.213	+
205	+++	0.174	+
206	++	2.0*	+
207	++	2.0*	+
208	+	37*	+
209	++	1.0*	+
210	++	2.0*	+

FIG.30B

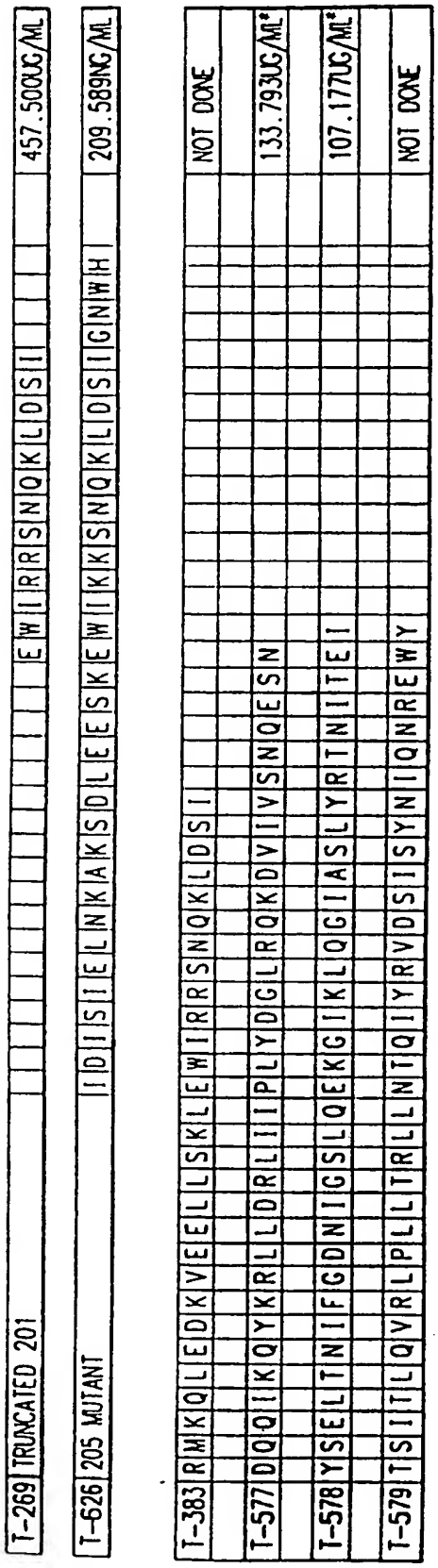


FIG.30C

FUSION ♥ALLMOTI5♥
PEPTIDE ♠107x178x4♠
.....RNKRGVFVLGFLGFLATAGSAMGAAS ♠♥ XXXXAQSRTLLAGIVQQQQQ

LLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKDQAQL♠NAWG♥ CAF

♥ALLMOTI5♥
*LVS PREDICTED COILED-COIL
RQVCHTTVPWPNASLTPDW *NND ♥TWQEWERKVDFLEENITALLEEAQIQQ

♠107x178x4♠
EKNMY ♠ELQKLNSWD* VF♥ GNXXXXXXXXXXXXXXXXXXXXXXXXXXX♠

IYIVMLAKLRQGYRPVFSSPPSYFQXTHTQQDPALPTREGKEGDGGEGGGNSSWP

WQIEYHF

FIG. 31

MTRRRVLSVVVLLAALACRLGAQTPEQPAPPATTVQPTATRQQTSFPFRVCELSSHGDLFRFSSD

♠ 107x178x4♠
IQCPSIGTRENHTEGLLMVFKDNIIPYSF ♠ KVRSYTKIVTNILIYNGWYADSVTNRHE♠

EKFSVDSY LTDQMDTIYQ CYNAVKMTKD GLTRVYVDRD GVNITVNLKP TGGLANGVRR

YASQTELYDA PGWLIWTYRT RTTVNCLITD MMAKSNSPFD FFVTTTGQTV EMSPFYDGKN

KETFHERADS FHVRTNYKIV DYDNRGTNPQ GERRAFLDKG TYTLSWKLEN RTAYCPLQIW

QTFDSTIATE TGKSIHFVTD EGTSSFVTNT TVGIELPDAF KCIEEQVNKT HEKYEAVQD

RYTKGQIAIT YFITSGGLLL AWLPLTPRSL ATVKNLTELT TPTSSPPSSP SPPAPSAARG

STPAAVLRRR RRDAGNATTP VPPTAPGKSL GTLNNPATVQ IQFAYDSLRR QINRMLGDLA

RAWCLEQKRQ NMVLRELTKI NPTTVMSSIY GKAVAAKRLG DVISVSQCVP VNQATVTLRK

SMRVPGSETM CYSRPLVSFS FINDTKTYEG QLGTDNEIFL TKKMTEVCQA TSQYYFQSGN

♠107x178x4♠
EIHVYNDYHH FKTIELDGIA TLQTFISLNT ♠SLIENIDFASLELYSRDEQRASNVFD *LE♠

LVS PREDICTED COILED COIL TM Potential
GIFREYNFQAQNIAGLRKDLDNAVSN* GRNQ FVDGLGELMDSLGSVG QSITN

♣P12LZIPC♣
TM Potential TM Potential
LVSTVGGLFSSLVSGFISF FK N ♣PFGGMLILVLVAGVVILVISL♣ TRRTRQMS

QQPVQMLYPG IDELAQQHAS GEGPGINPIS KTELQAIMLA LHEQNQEQKR AAQRAAGPSV

ASRALQAARDRFPGLRRRRY IIDPETAAALL GEALTEF

FIG. 32

MMDPNSTSLD VKFTPDPYQV PFVQAFDQAT RVYQDLGGPS QAPLPCVLWP VLPEPLPQGQ

LTAYHVSTAP TGSWFSAPQP APENAYQAYA APQLFPVSDI TQNQQTNQAG GEAPQPGDNS

TVQTAAAVVF ACPGANQGQQ LADIGVPQPA PVAAPARRTR KPQQPESLEE CDSELCI

@DNA BINDING@ ♠107x178X4♠ +DIMERIZATION+
@KRY KNRVASRKCRAK ♠FK@ Q +LLQHYREVAAAKSSENDRLRLLLKQ♠

MCPSLDVD+ SI IPRTPDVLHE DLLNF

FIG. 33

FUSION
PEPTIDE ♥ALLMOTI5♥ *LVS COILED-COIL*
FAG ♥VVLAGAALGVATAAQITAGIALHQSML*NSQAIDNLRASLETTN

QAIEAIRQAGQEMI*LAVQGVQDYINN♥ ELIPSMNQLSCDLIGQKLGLKLLRYYT

♣P23LZIPC♣
♣P6.12LZIPC♣
♠107X178X4♠
♥ALLMOTI5♥
CIISLIGPSLRD ♣PISA ♠♥EISIQLSYALGGDINKV♣ LEKLGYSGGDL♣

♣P1.12LZIPC♣
LGILES♠ RGIKARI♥ THVDTESYFIVLSIAY ♣PTLSEIKGVIVHRLEGV♣ SY

NIGSQEWYTTVPKYVATQGYLISNFDESSCTFMPEGTVCSQNALYPMSPLLQECL

RGSTKSCARTLVSGSFGNRFILSQGNLIANCASILCKCYTTGTIINQDPDKILTYIAA

♣P23LZIPC♣
♣P12LZIPC♣
♥ALLMOTI5♥
LVS COILED-COIL
DHCPVVEVNGVTIQVGSRRYPDAVYLHRIDLGP ♣P ♥IS *LERLDVGTNLGN

♦TRANSMEMBRANE REGION♦
AIAKLEDAKELL♣ ESSDQI*L♣ RSMK ♦GLSSTSIVYILI♥ AVCLGGLIGIP

ALICCC♦ RGRCNKKGEQVGMSRPGLKPDLTGTSKSYVRSL -

FIG. 34

Pre S1 and Pre S2
MGQNLSTSNPLGFFPDHQLDPAFRANTANPDWDFNPNKDTWPDANKVGAGAFG

LGFTPPHGGLLGWSPQAQGILQTLPANPPPASTNRQSGRQPTPLSPPLRNTHPQAM

QWNSTTFHQTLQDPRVRGLYFPAGGSSSGTVNPVLTTASPLSSIFSRIGDPALN

MAJOR SURFACE ANTIGEN(LHBs)
FUSION
PEPTIDE
♣P12 & 23LZIPC♣
MENITSG FLG ♣PLL VLQAGFFLLTRILTI♣ PQSLDSWWTSLNFLGGTTVCLG

♣P12 & 23LZIPC♣
QNSQSPTSNHSPTSCPPTC ♣PGYRWMCLRRFIIFLFILLLCLIFLLVLLDYQGML♣

PVCPLIPGSSTTSTGPCRTCMTTAQGTSMYPSCCCTKPSDGNCTCIPIPSSWAFGKF

♦TRANSMEMBRANE REGION♦
LWEWASARFSWLS ♦LLVPFVQWFVGLSPTVWLSVI♦ WMMWYWGPSL

♦TRANSMEMBRANE REGION♦

♦YSILSPFLPLLPIFFCLWVYI♦

FIG. 35

FUSION ♥ ALLMOTIF ♥ ♠107x 178x4♠
PEPTIDE *LVS COILED COIL
AIQLIPLFVG LGI ♥ITTAVSTGAAGLGVS ♠IT *QYTKLSHQLISDV

QAISSTIQDLQDQVDSLAEVVLQ* NRRGLDLLTAE♠ QGGI♥

CLALQEKCCFYANKSGIVRDKIKNLQDDLERRRRQLIDNPFWTSFHG

FLPYVMPLLGPLLCLLLVLSFGPIIFNKLMTFIKHQIESIQAKPIQVHYII

TRANSMEMBRANE REGION
RLEQEDSGGSYLTLT.....??????????????????????????....

FIG. 36

MKAQKGFTLI ELMIVVAIIG ILAAIAPGQ

♠107x178x4♠
♥ALLMQTI5♥
♠♥YQDYTARTQVTRAVSEVSALKTAAESAILEGKEIVSSA♠ T♥

PK DTQYDIGFT

♠107x178x4♠
♥ALLMQTI5♥
♠♥ESTLLDGSGKSQIQVTDNQDGTVELVATLGKSSGS♠ AIKGAVITSR♥

KNDGV WNCKITKTPT AWKPNYAPAN CPKS

FIG. 37

MNTLQKGFTL IELMIVIAIV GILAAVALPA YQDYTARAQV

SEAILLAEGQ KSAVTEYYLN HGIWP

♠107x178x4♠
♥ALLMQTI5♥
♠♥KDNTSAGVASSSSIKGKYVKEVKVENGVVTAT♠

MNSSNVNKEIQGKKLSLWAKRQDGSVKW♥

FCGQP VTRNAKDDTV TADATGNDGK IDTKHLPSTC RDNFDAS

FIG. 38

MKKTLLGSLI LLAFAGNVQA DINTETSGKV TFFGKVVENT

CKVKTEHKNL SVVLNDVGKN SLSTKVNTAM PTPFTITLQN

CDPTTANGTA NKANKVGLYF Y

♠107x178x4♠
♥ALLMOTI5♥
♠♥SWKNVDKENNFTLKNEQTTADYATNVNI♠

QLMESNGTKAISVVGKETE♥

DF MHTNNNGVAL NQTHPNNAHI SGSTQLTTGT NELPLHFIAQ

YYATNKATAG KVQSSVDFQI AYE

FIG. 39

MNKKLLMNFF IVSPLLLATT ATDFTPVP

♠107x178x4♠
♥ALLMOTI5♥
♠♥LSSNQIIKTAKASTNDNIKDLLDWYSSGSDTFTNS♠♥

EVLDNSL GSMRIKNTDG SISLIIFPSP YYSPAFTKGE KV

♠107x178x4♠
♠DLNTKRTKKSQIITSEGTYIIIFQISGVT♠

N TEKLPTPIEL PLKVKVHGKD SPLKYG

♣P12LZIPC♣
♣PKFDKKQLAISTLDFEIRHQLTQI♣

IIGLYRSSDKT GGYWKITMND GSTYQSDLSK KFEYNTEKPP

INIDEIKTIE AEIN

FIG. 40

♥ALLMOTIS♥
MKKTAFILLL FIALTLTTSP L ♥VNG

♠107x178x4♠
LVS PREDICTED COILED-COIL
S ♠EKSEEINEKDLRKKSELQRNALSNLRQIY YYNEKAITENKESDD♠

QFLENTLL♥ FKG FFTGHPW

♠107x178x4♠
♠YNDLLVDLGSKDATNKYKGKKVDLYGAY♠

YGYQCAGGTPNKTACMYGGVTLHDN NRLTEEKKVP INLWIDGKQTTV

♣P12LZIPC♣
♣PIDKVKTSKKEVTVQELDL♣ QARHYLHGK FGLYNSDSFGGKVQ

♣P12LZIPC♣
RGLIVF HSSEGSTVSY DLFDAQGQY ♣P DTLLRIYRDN KTINSENLHI♣

DLYLYTT

FIG. 41

♥ALLMOTI5♥
MKKTAFTLLL FIALTLTTSP L ♥VNGS

♠107x178x4♠
♠EKSEEINEKDLRKKSELQGTALGNLKQIYYYNEKAKTENKESHD♠ Q♥

FLQIITILFKG FFTDHSWYND LLVDFDSKDI VDKYKGKKVDLYGAYY

GYQC AGGTPNKTAC MYGGVTLHDN NRLTEEKKVPINL WLDGKQNTV

♠107x178x4♠
♥ALLMOTI5♥
♣P12LZIPC♣
♣P ♥L ♠ETVKTNKKNVTVQELDLQARRYL♣ QEKYNLYN♠

SDVFDGKVQR♥ GLIVF HTSTE

♣P23LZIPC♣
♣PSVNYDLFGAQGQYSNTLLRIYRDNKTINSENMHI♣ DIYLYTS

FIG. 42

MKNITFIFFILLASPLYANGDRLYRADSRPPDEIKRFRSLMPRGNEYFDRGT

♥ALLMOTI5♥
♥QMNINLYDHARGTQTGFVRYDDGYV

♠107x178x4♠
♠STSLSLRSAHLAGQYILSGYSLTIYIVI♠ ANMFNVNDVISVY♥

SP IIPYEQEVSAL GGIPYSQIYG WYRVNFGVID ERLHRNREYR

DRYYRNLNIA PAEDGYRLAG FPPDHQAWRE EPWIHHAPQG

CGDSSRTITG DTCNE

♥ALLMOTI5♥
♥IETQNLSTIYLREYQSKVKRQIFSDYQSEVDIYNRIRDEL♥

FIG. 43

MMFSGFNADY EASSSRCSSA SPAGDSLSYY HSPADSFSSM

GSPVNAQDFC TDLAVSSANF IPTVTAISTS PDLQWLVQPA

LVSSVAPSQT RAPHPFGVPA PSAGAYSRAG VVKTMTGGRA

LVS PREDICTED COILED-COIL

QSIGRRGKVE QLSPEEEEKR RIRRE *RNKMA AAK

♠107x178x4♠

♥ALLMOTIS♥

♥CRNRRREL ♠TDTLQAETDQLEDEKSALQTEIANLLKEKEKL♥

EFILAAHR* PACKIPDDL GFPEEMSVAS LDLTGGLPEV

ATPESEEAFT LPLLNDPEPK PSVEPVKSIS SMELKTEPFD

DFLFPASSRP SGSETARSVP DMDLSGSFYA LPLLNDPEPK

PSVEPVKSIS SMELKTEPFD DFLFPASSRP SGSETARSVP

DMDLSGSFYA GSSSNEPSSD SLSSPTLLAL

FIG. 44

SGWESYYKTEGDEEAEEEQEENLEASGDYKYSGRDSLIFLVDASKA

MFESQSEDELTPFDMSIQCIQSVYISKIISSDRDLLAVVFYGTEKDKNS

VNFKNIYVLQELDNPGAKRILELDQFKGQQGQKRFQDMMGHGSDY

SLSIEVLWVCANLFSDVQFKMSHKRIMLFTNEDNPHGNDSAKASRAR

TKAGDLRDTGIFLDLMHLKKPGGFDISLFYRDIISIAEDED

♠107x178x4♠
♥ALLMOTI5♥
LVS PREDICTED COILED-COIL

♥LRVH *FEE ♠SSKLEDLLRKVRAKETRKRALSRLKLKLNKDIV* ISV

GIYNLVQKAL♥ KPPPIKLYRETN♠ EPVKTKTRTFNTSTGGLLLPSDTKR

SQIYGSRQIILEKEETEELKRFDDPGLMLMGFKPLVLLKKHHLRPSLFVYPE
ESLVIGS STLFSALLIKCLEKEVAALCRYTPRRNIPPYFVALVPQEEELDDQK
IQVTPPGFQLVFLPFADDKRKMPFTEKIMATPEQVGKMKAIVEKLRFTYRS
DSFENPVLQQIFRNLEALALDLME

♣PI2LZIPC♣
♣PEQAVDLTLPKVEAMNKRL♣ GSLVDEFKELVYPPDYNPEGKVTKR
KHDNEGSGSKRPKVEYSEEELKTHISKGTLGKFTVPMLKEACRAYGLKSG
LKKQELLEALTKHFQD

FIG. 45

GGGALSPQHSAVTQGSHKNKEGMDAKS

♠107x178x4♠
♥ALLMOTI5♥
♥♠LTAWSRTLVTFKDVFVDFTREEWKLLDT♠ AQQIVYRNV
MLENYKNLVSLGYQLT♥ KPDVILRLEKGEEPWLVEREIHQETHPD
SETAFEIKSSVSSRSIFKDKQSCDIKMEGMARNDLWYLSLEEVWKCR
DQLDKYQENPERHLRHQLIHTGEKPYECKECGKSFSRSSHLIGHQKT
HTGEEPYECKECGKSFSWFSHLVTHQRTHTGDKLYTCNQCGKSFVH
SSRLIRHQRTHTGHKPYECPECGKSFRQSTHLILHQRTHVRVRPYECN
ECGKSYSQRSHLVVHHRIHTGLKPFECKDCGKCFSRSSHLYSHQRTH
TGEKPYECHDCGKSFSQSSALIVHQRIHTGEKPYECCQCGKAFIRKN
DLIKHQRIHVGAETYKCNQCGHFSQNS

♣P23LZIPC♣
♣PFIVHQIAHTGEQFLTCGNQCGTALVNTSNLIGQTNHI♣ RENAY

FIG. 46

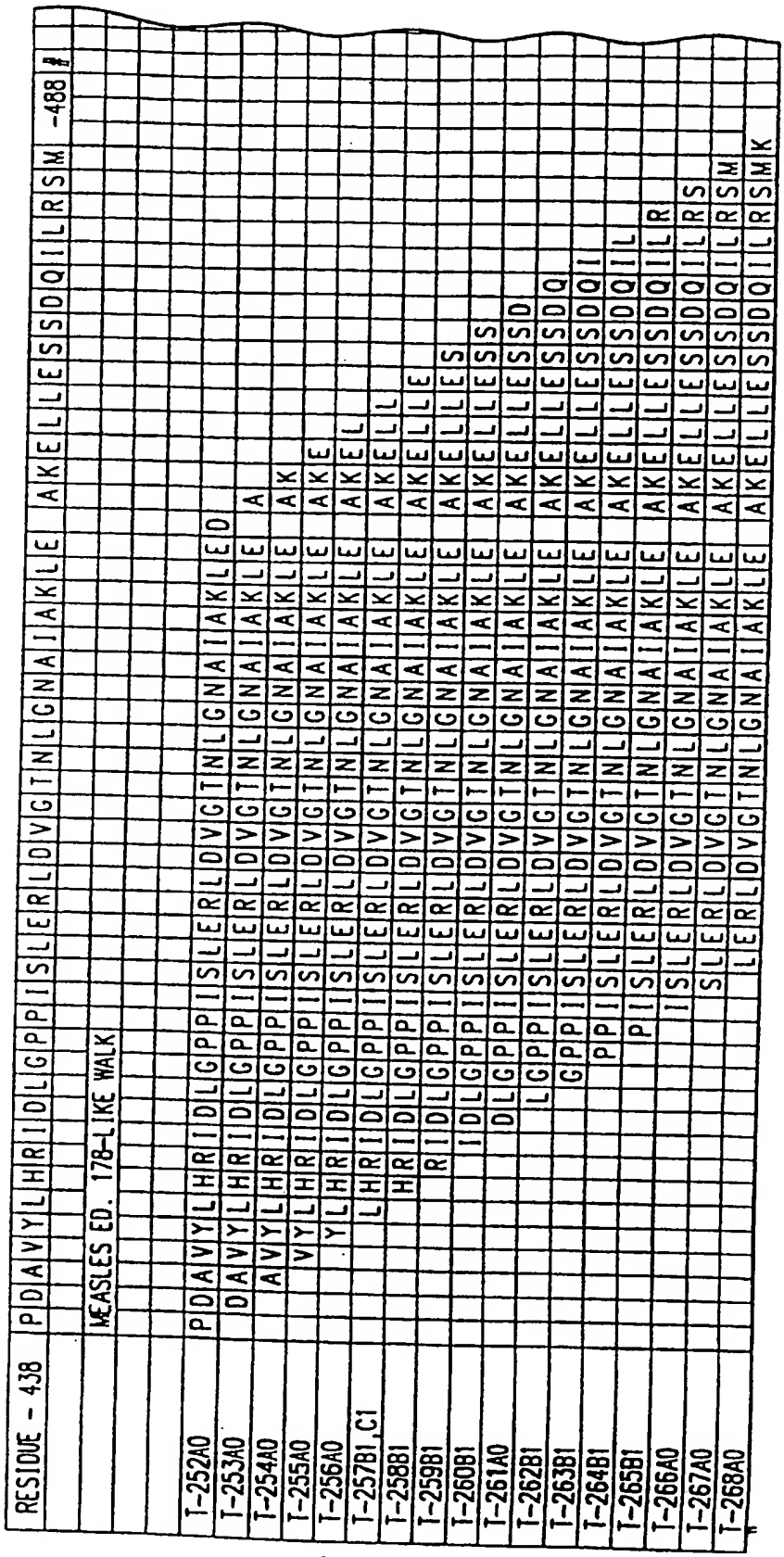
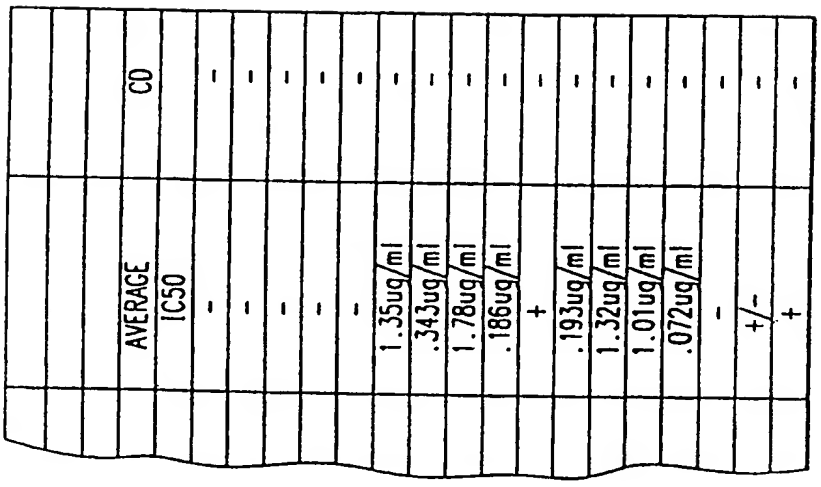


FIG.47A



AVERAGE IC50	CD
-	-
-	-
-	-
-	-
-	-
1.35ug/ml	-
.343ug/ml	-
1.78ug/ml	-
.186ug/ml	-
+	-
.193ug/ml	-
1.32ug/ml	-
1.01ug/ml	-
.072ug/ml	-
-	-
+/-	-
+	-

FIG.47B

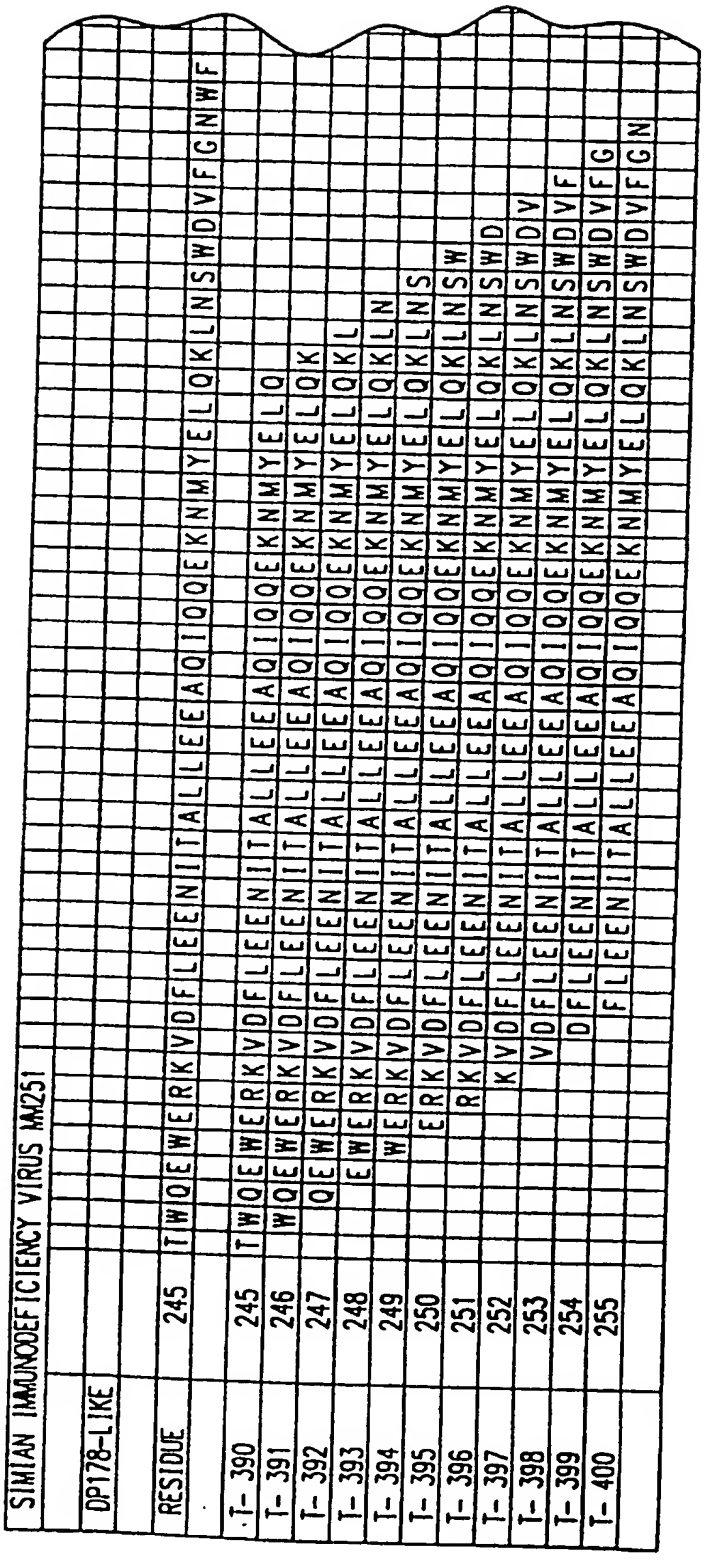


FIG.48A

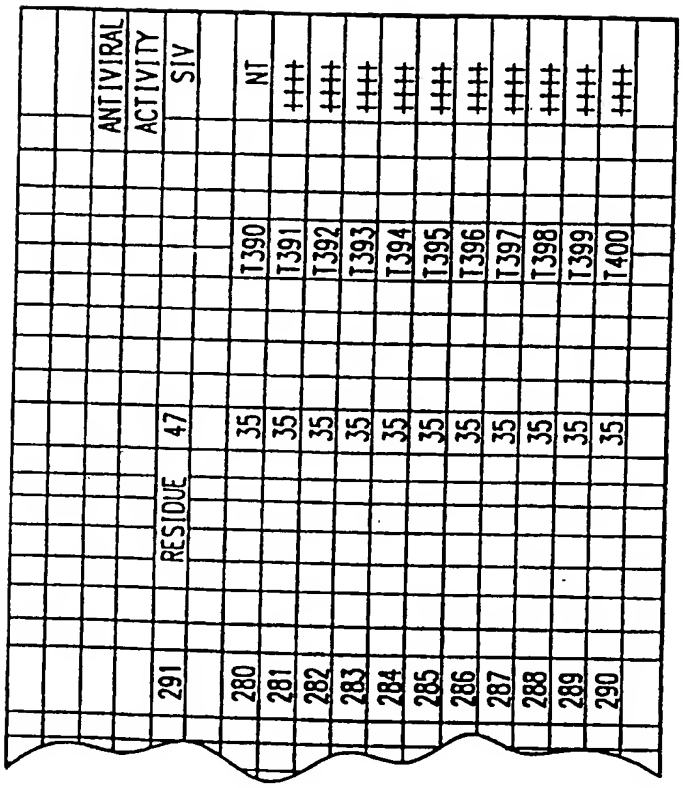


FIG.48B

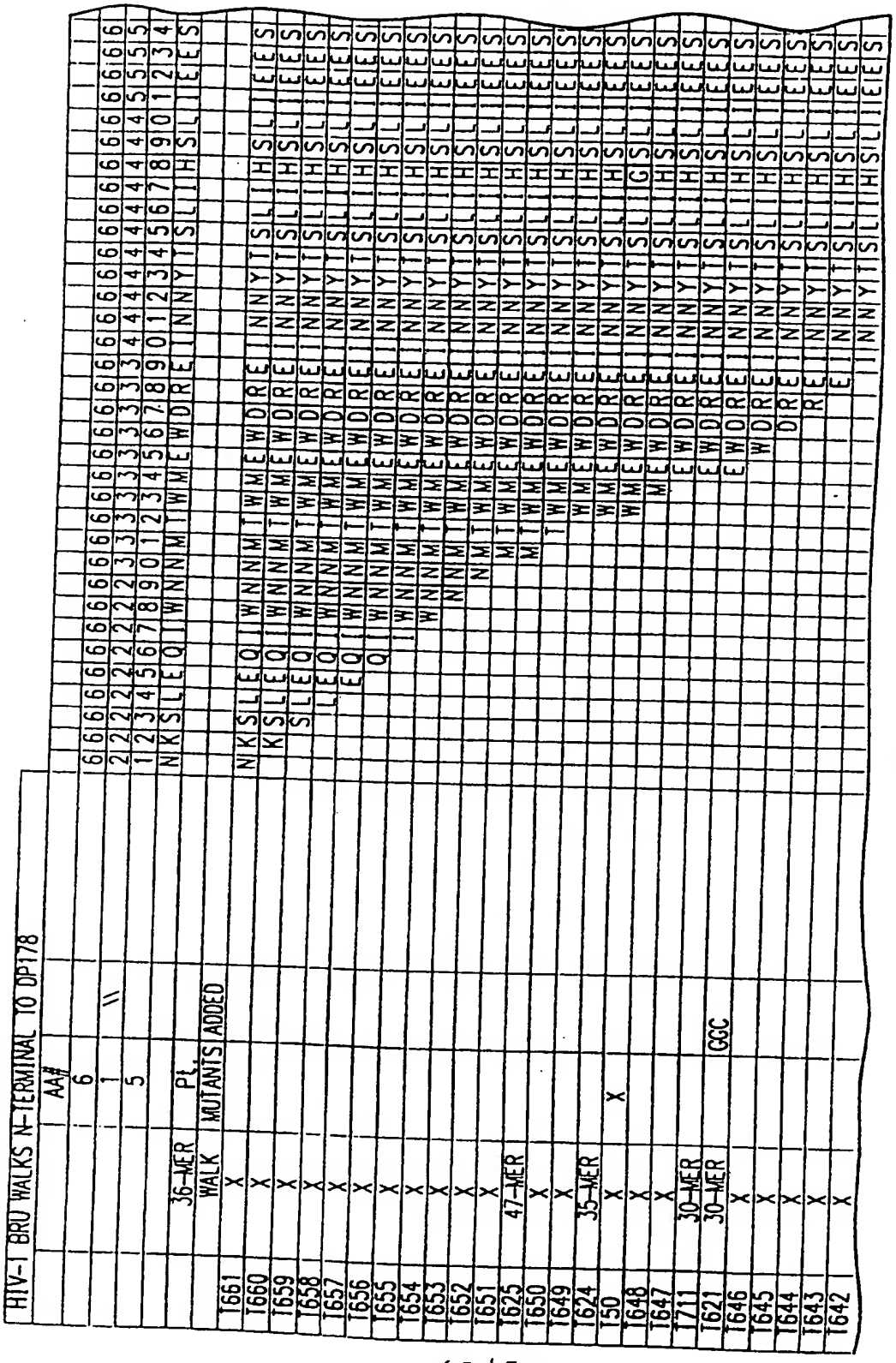
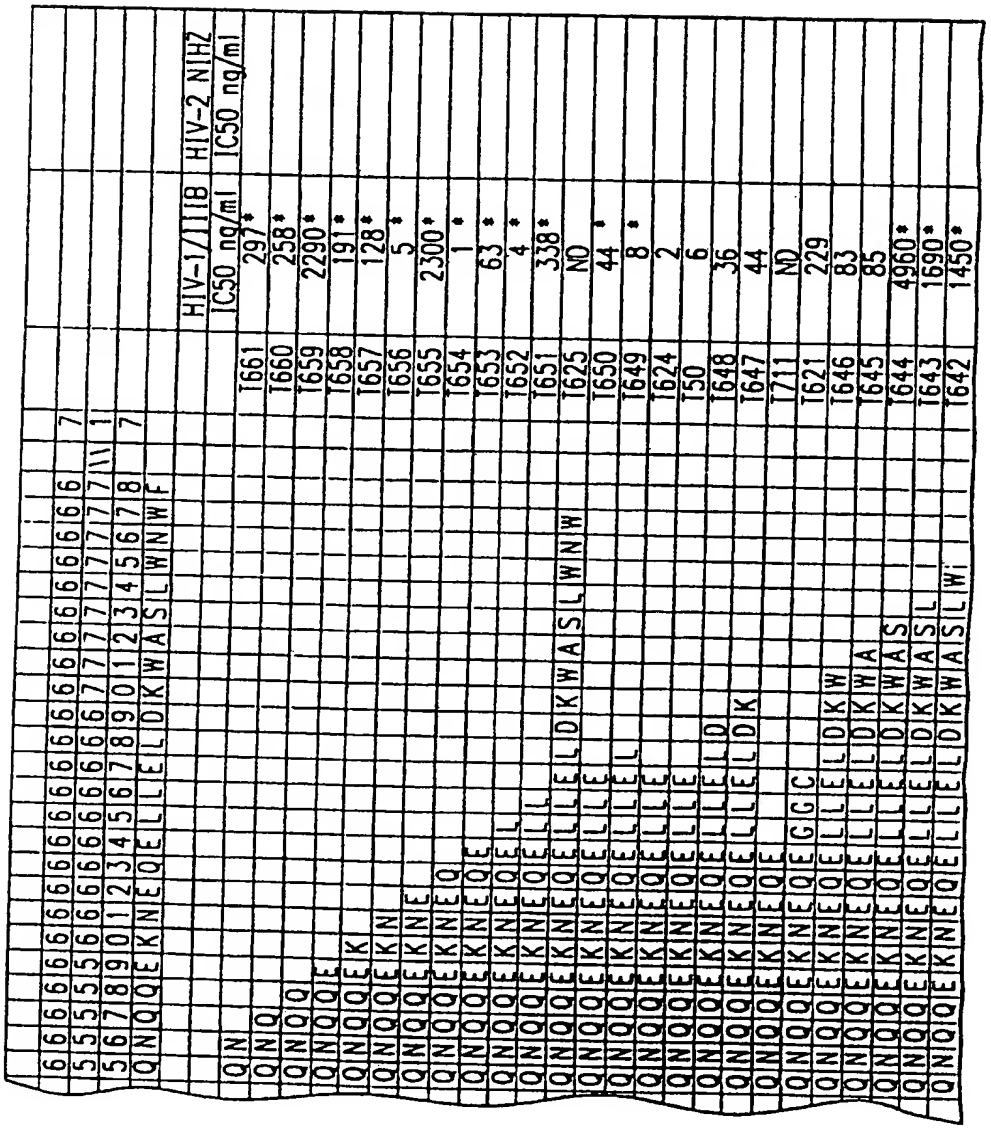


FIG.49A



	HIV-1/IIIB IC50 ng/ml	HIV-2 NIHZ IC50 ng/ml
T661	297*	
T660	258*	
T659	2290*	
T658	191*	
T657	128*	
T656	5*	
T655	2300*	
T654	1*	
T653	63*	
T652	4*	
T651	338*	
T625	ND	
T650	44*	
T649	8*	
T624	2	
T50	6	
T648	36	
T647	44	
T711	ND	
T621	229	
T646	83	
T645	85	
T644	4960*	
T643	1690*	
T642	1450*	

FIG.49B

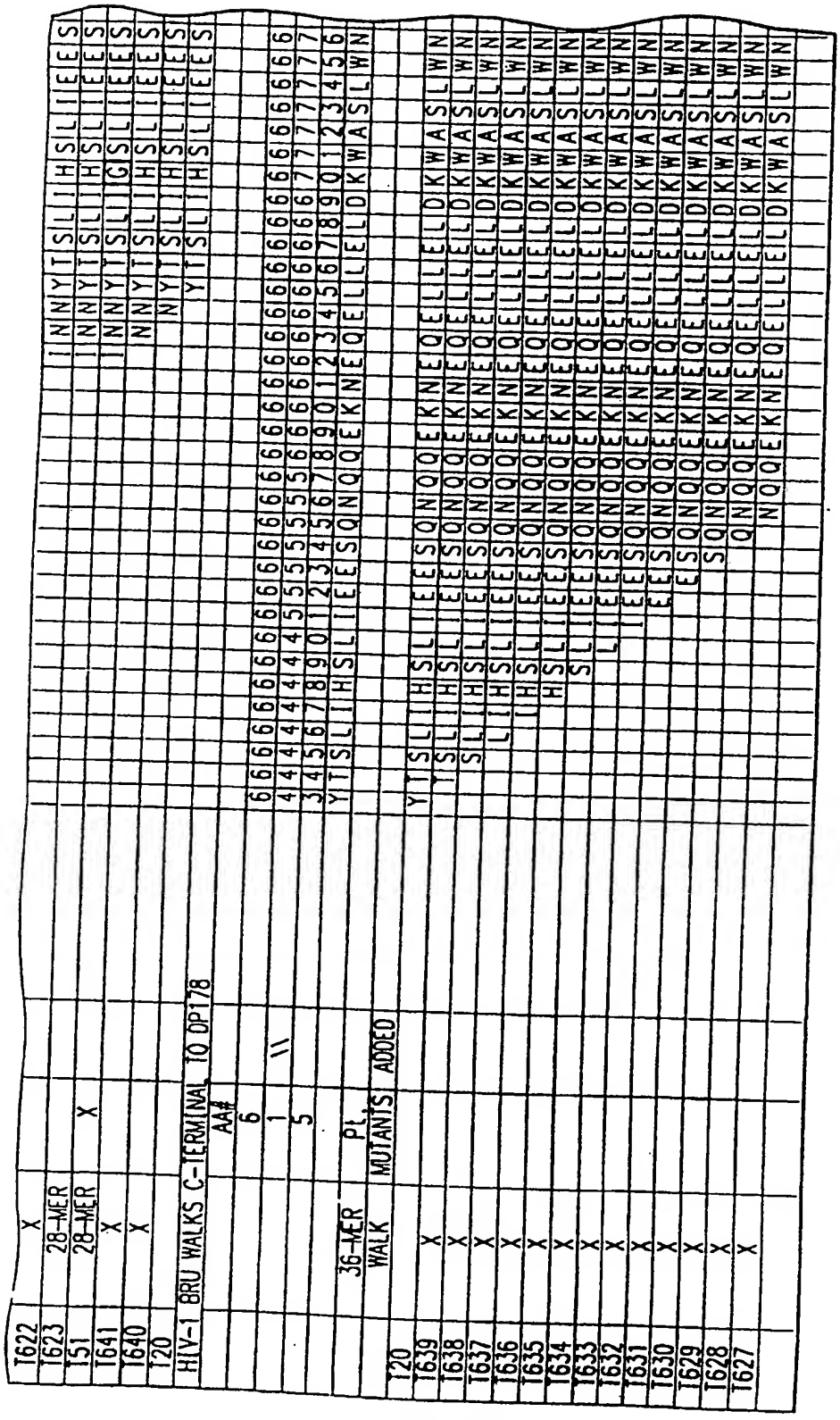


FIG.49C

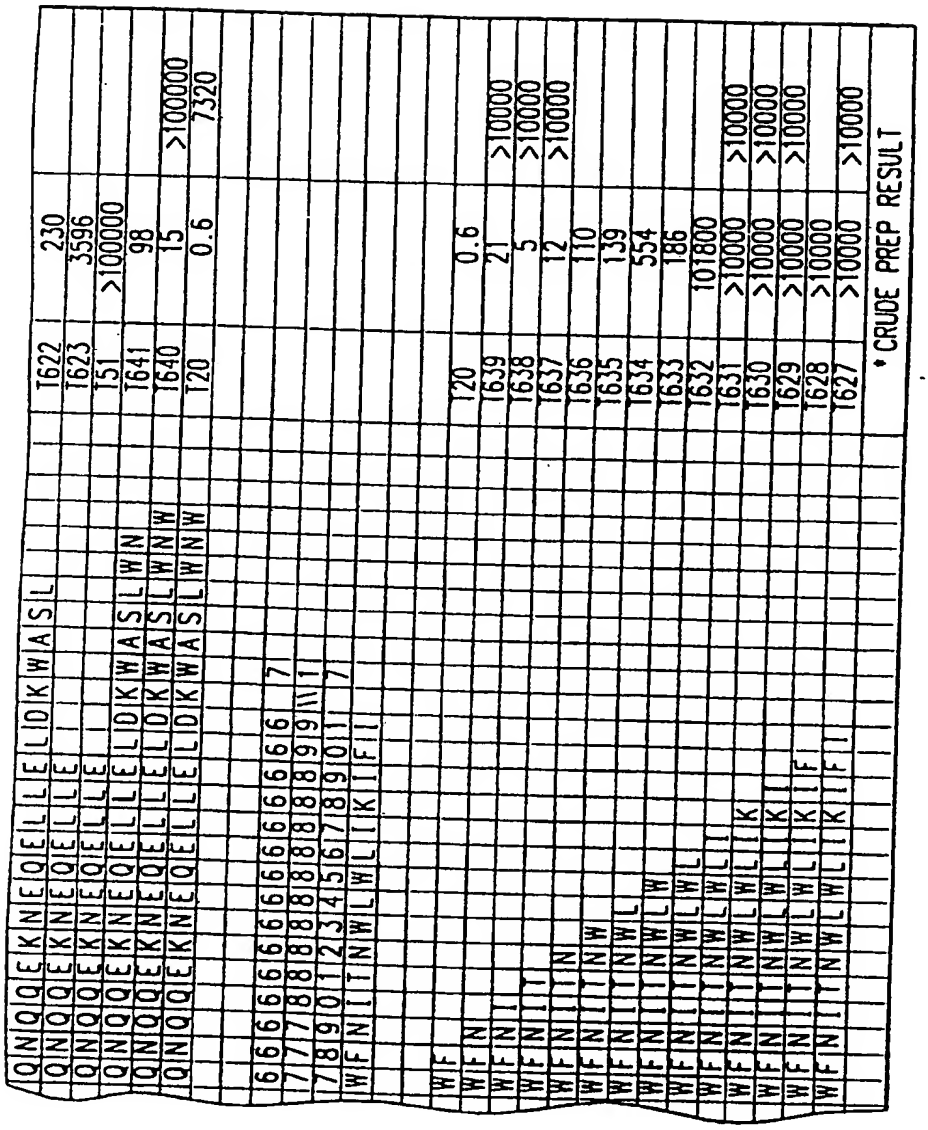


FIG.49D

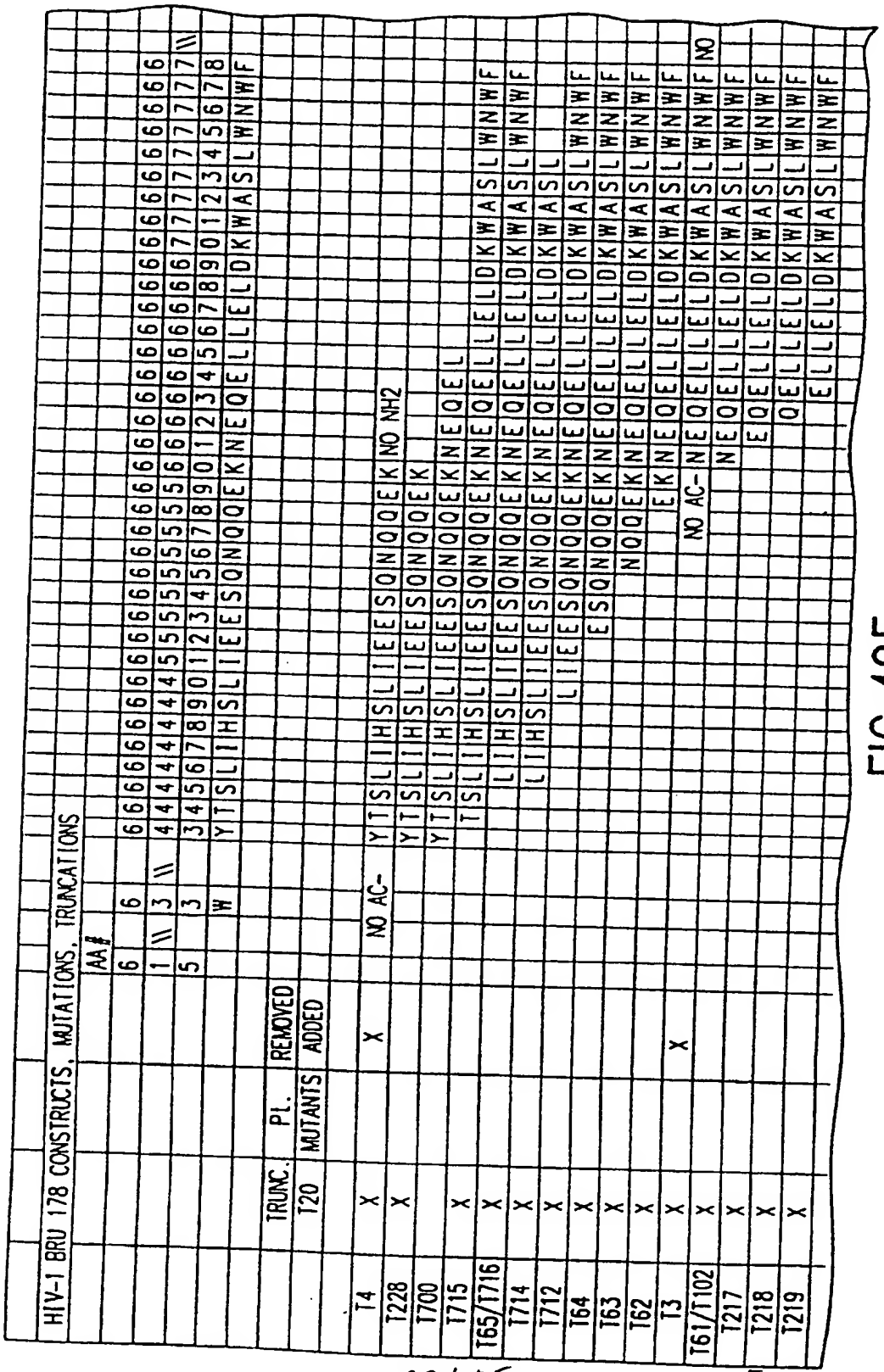
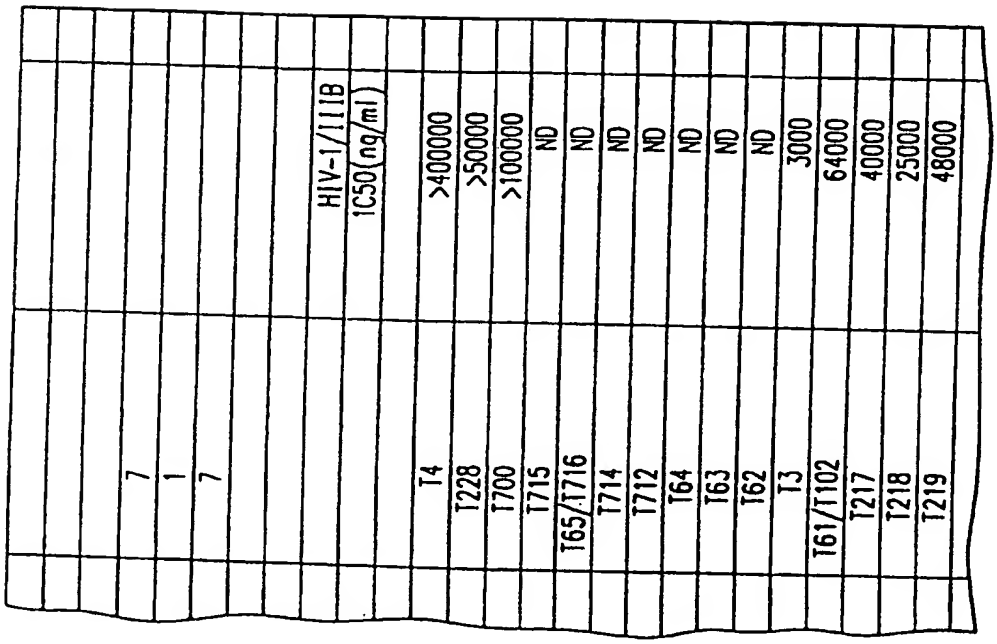


FIG.49E



		HIV-1/111B IC50(ng/ml)
7	T4	>400000
1	T228	>50000
7	T700	>100000
	T715	ND
	T65/T716	ND
	T714	ND
	T712	ND
	T64	ND
	T63	ND
	T62	ND
	T3	3000
	T61/T102	64000
	T217	40000
	T218	25000
	T219	48000

FIG.49F

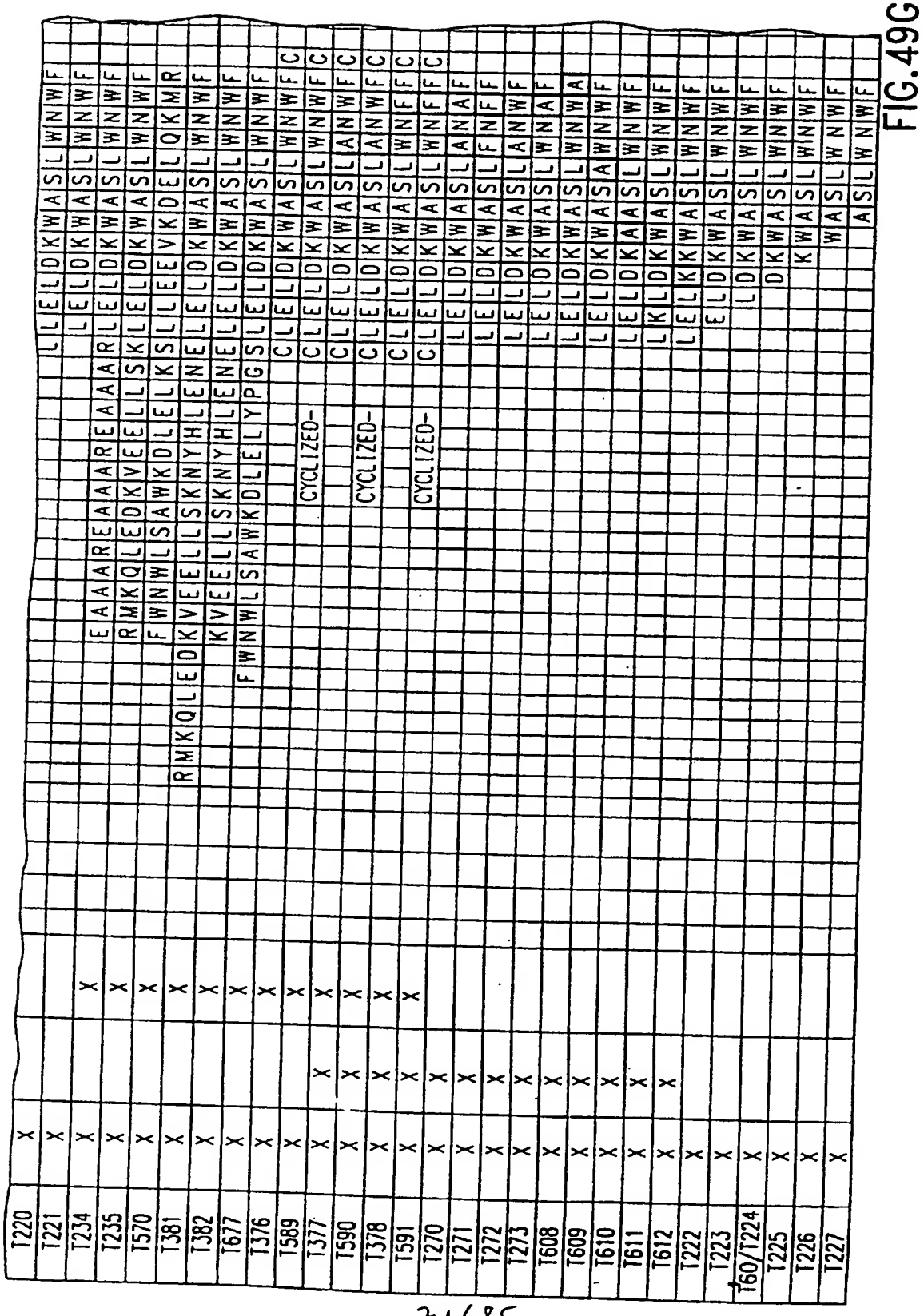
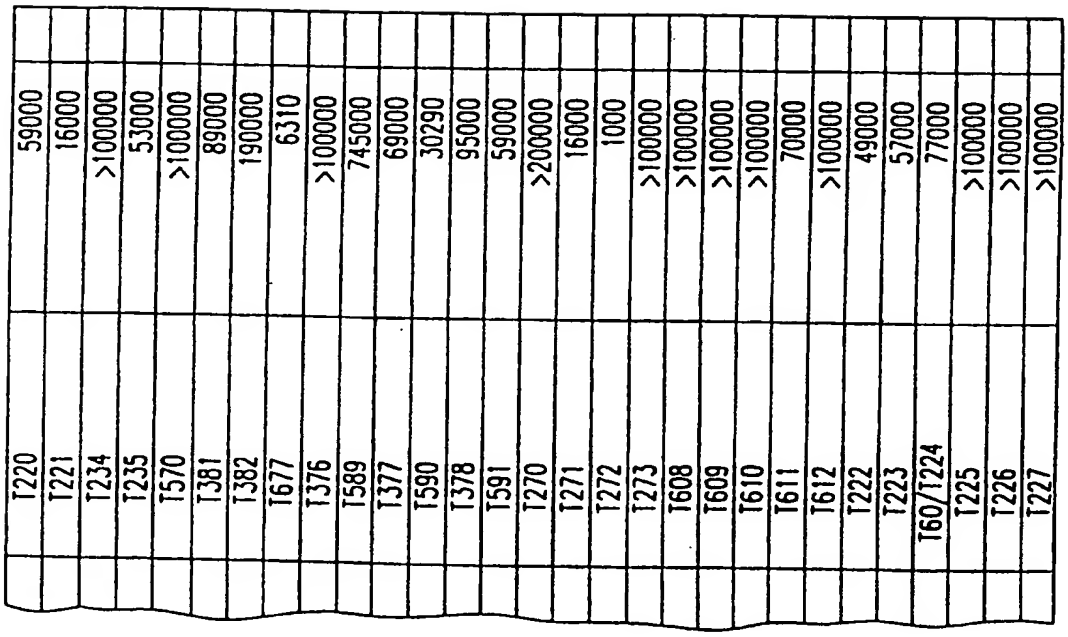


FIG.49G



T220	59000
T221	16000
T234	>100000
T235	53000
T570	>100000
T381	89000
T382	190000
T677	6310
T376	>100000
T589	745000
T377	69000
T590	30290
T378	95000
T591	59000
T270	>200000
T271	16000
T272	1000
T273	>100000
T608	>100000
T609	>100000
T610	>100000
T611	70000
T612	>100000
T222	49000
T223	57000
T60/T224	77000
T225	>100000
T226	>100000
T227	>100000

FIG.49H

HIV-1 Bru 178 CONTRUCTS, MUTATIONS														
			AA# 615 \\ 633 \\	643	644	645	646	647	648	649	650	651	652	653	654
			W	Y	T	S	L	I	H	S	L	I	E	E	S
	Pt. MUTANTS	REMOVED ADDED													
T595		X	C G G	Y	T	S	L	I	H	S	L	I	E	E	S
T574		X	C13H27CO-	Y	T	S	L	I	H	S	L	I	E	E	S
T680		X	FREE TERMINI	Y	T	S	L	I	H	S	L	I	E	E	S
T573		X	NO AC-	Y	T	S	L	I	H	S	L	I	E	E	S
T84		X	DIG-	Y	T	S	L	I	H	S	L	I	E	E	S
T83		X	BIOTIN-	Y	T	S	L	I	H	S	L	I	E	E	S
T708		X	BIOTIN-NH(CH2)6CO-	Y	T	S	L	I	H	S	L	I	E	E	S
T707		X	BIOTIN-NH(CH2)4CO-	Y	T	S	L	I	H	S	L	I	E	E	S
T20				Y	T	S	L	I	H	S	L	I	E	E	S
T95	X			Y	T	S	L	I	H	S	L	I	E	E	S
T96	X			Y	T	S	L	I	H	S	L	I	E	E	S
T97	X			Y	T	S	L	I	H	S	L	I	E	E	S
T98	X			Y	T	S	L	I	H	S	L	I	E	E	S

FIG.49I

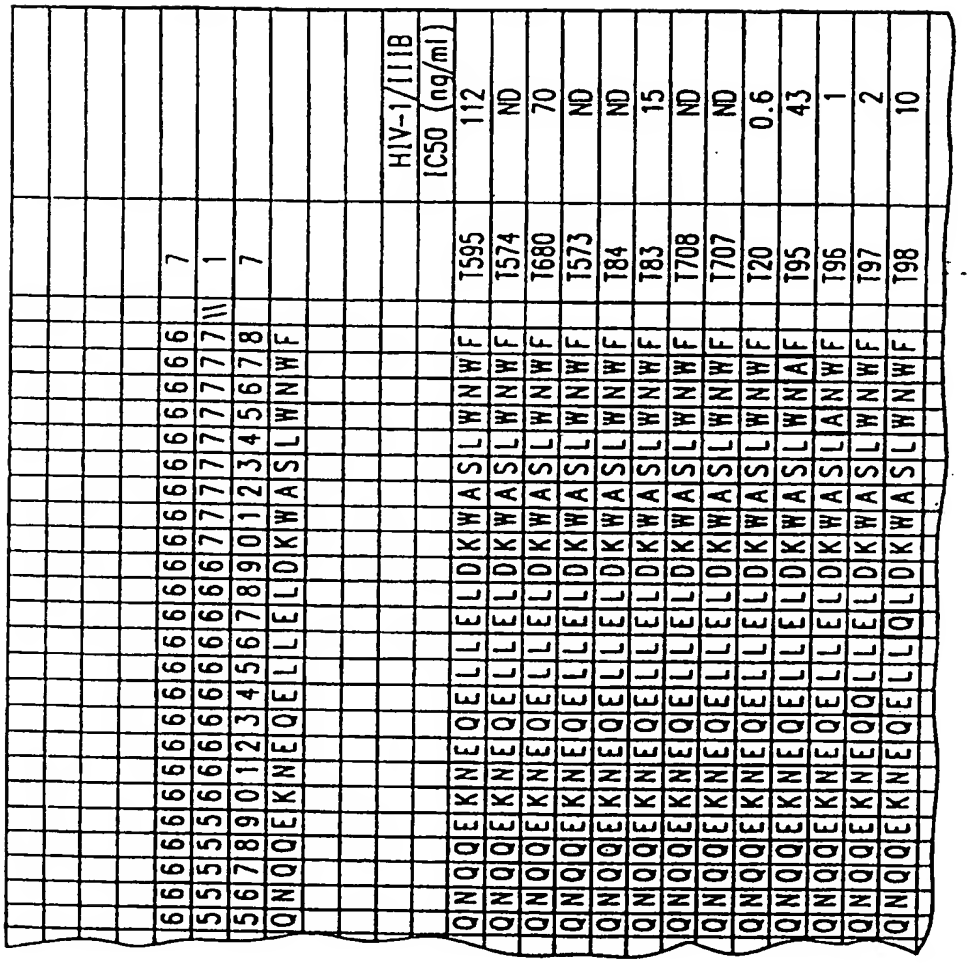


FIG.49J

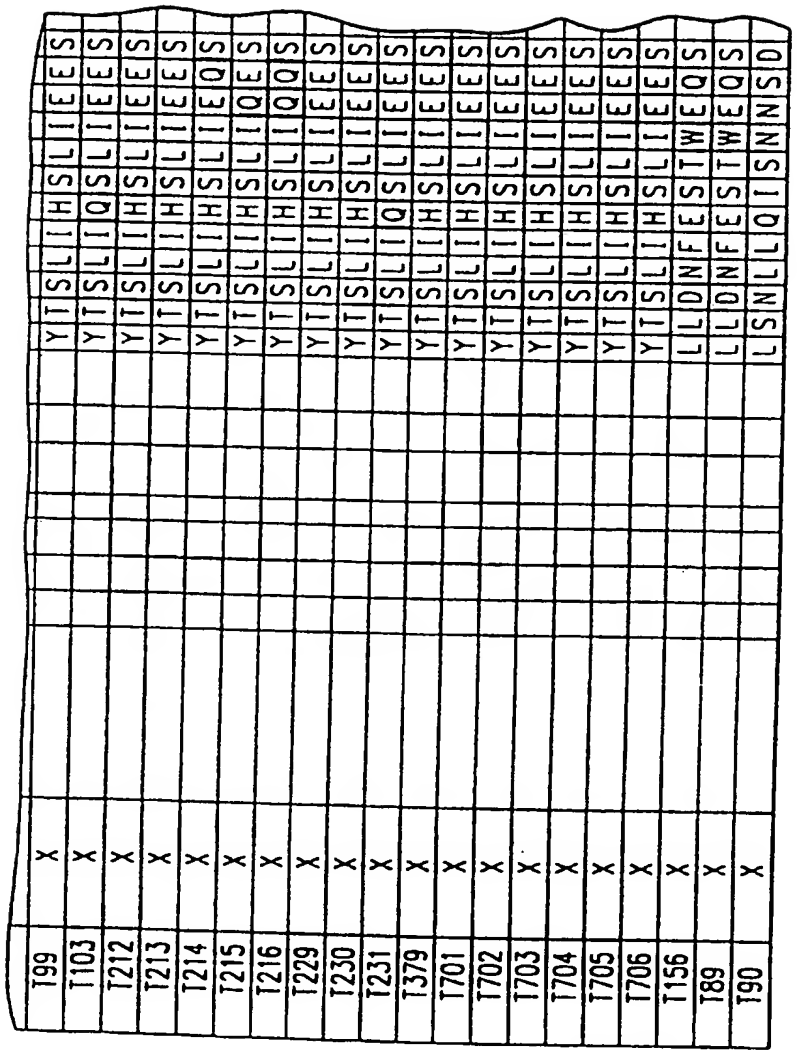


FIG.49K

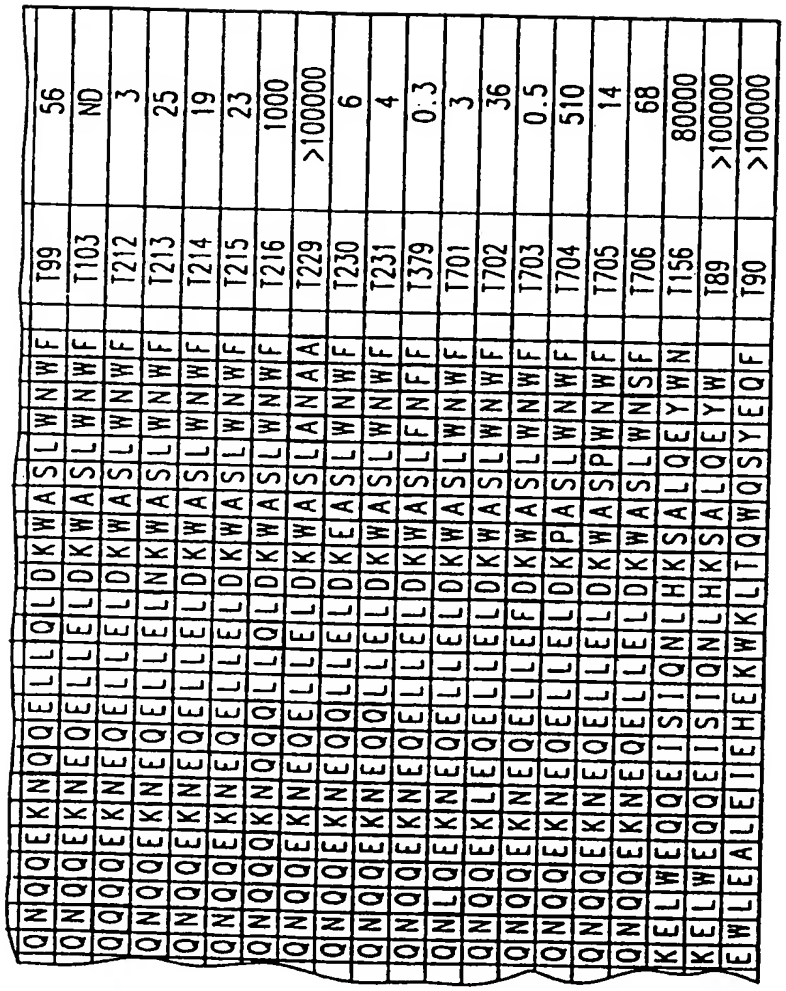


FIG.49L

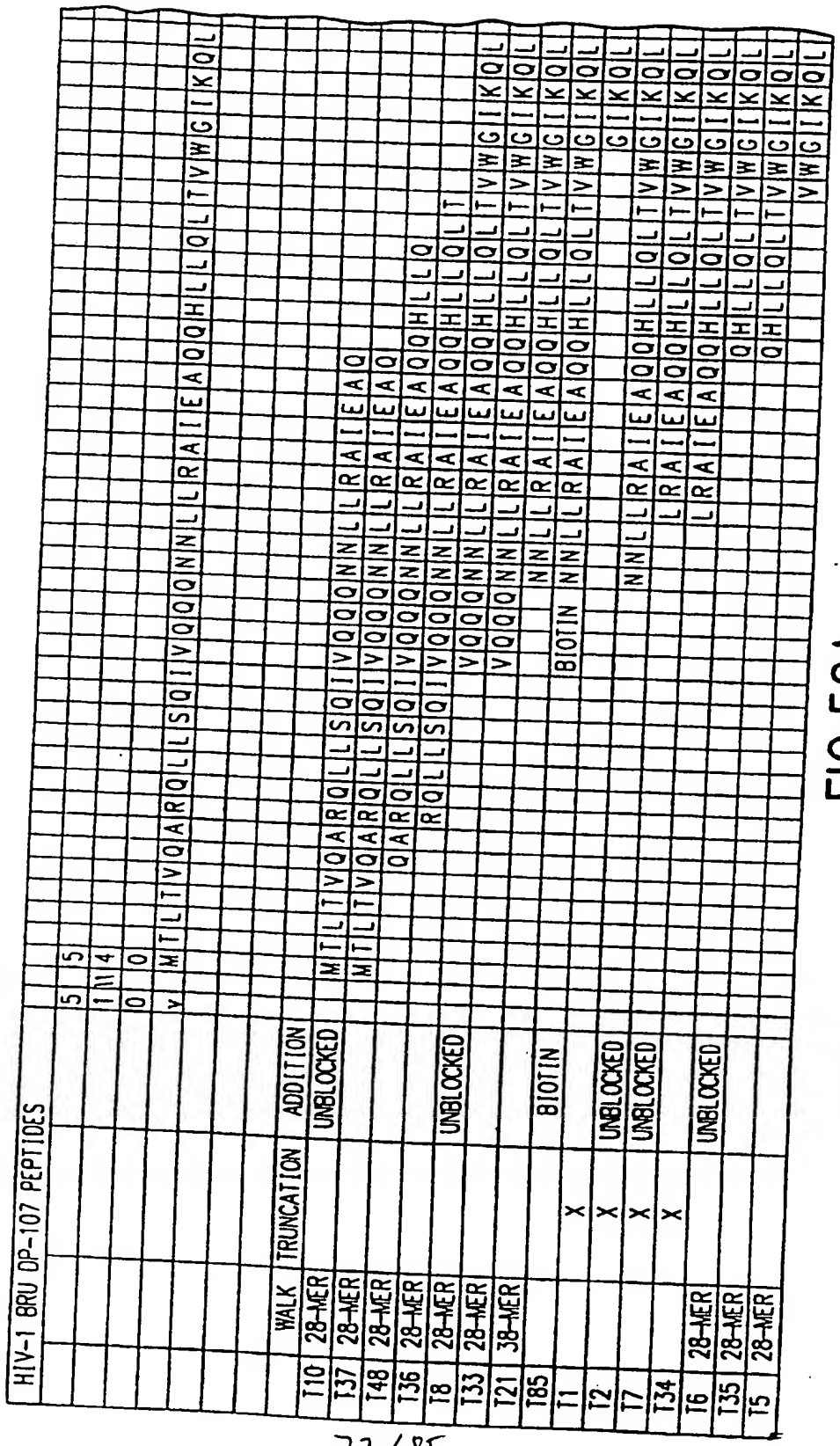


FIG.50A

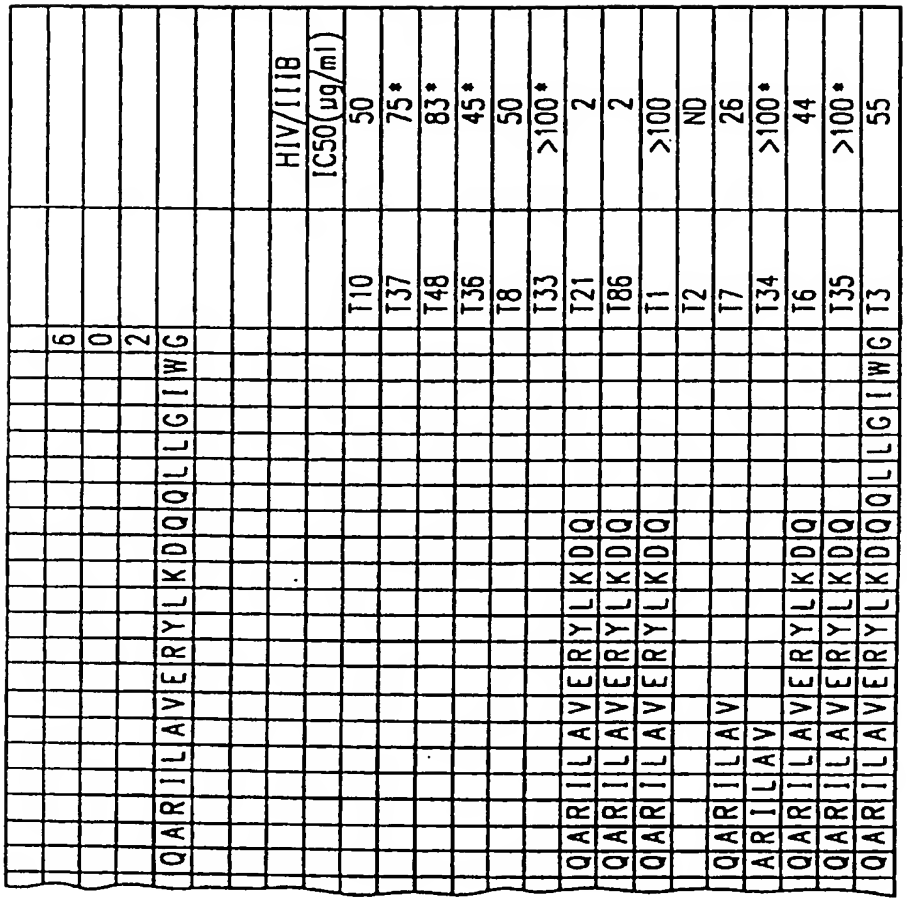


FIG.50B

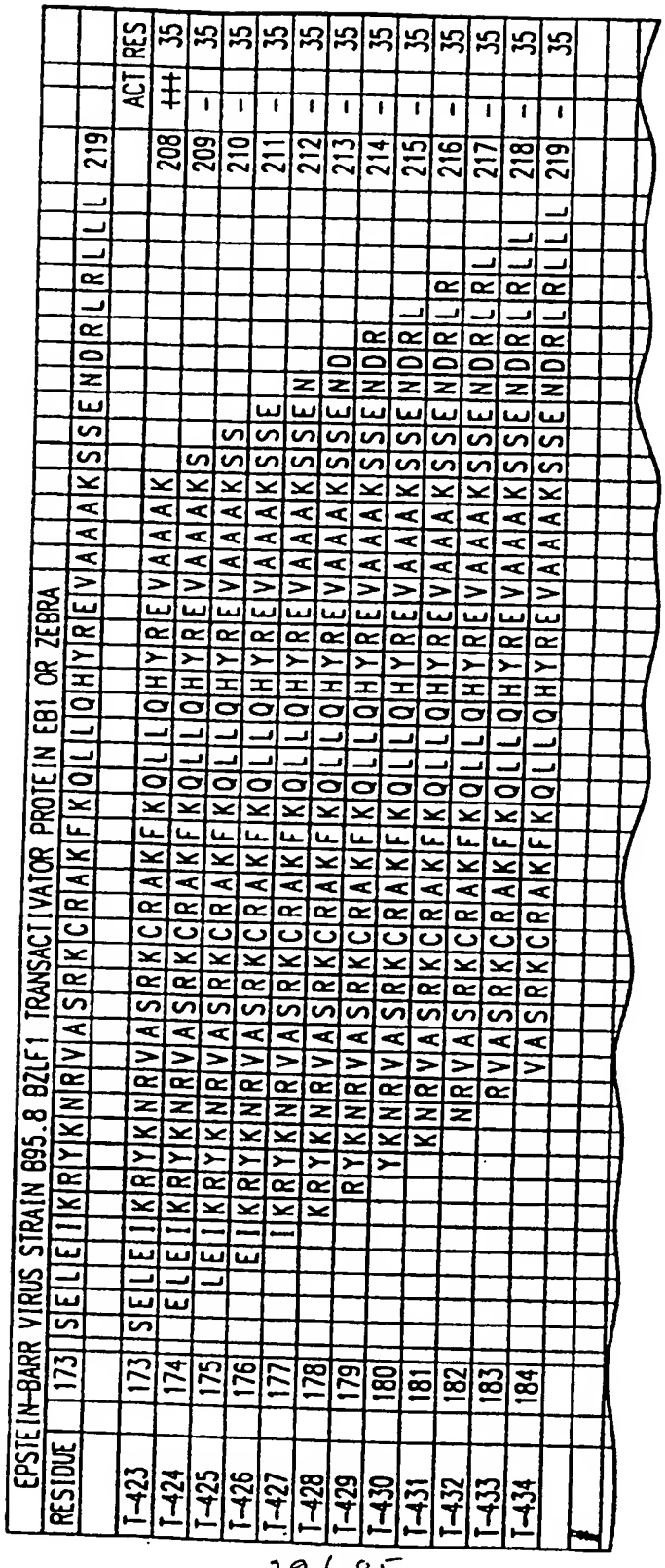


FIG.51A

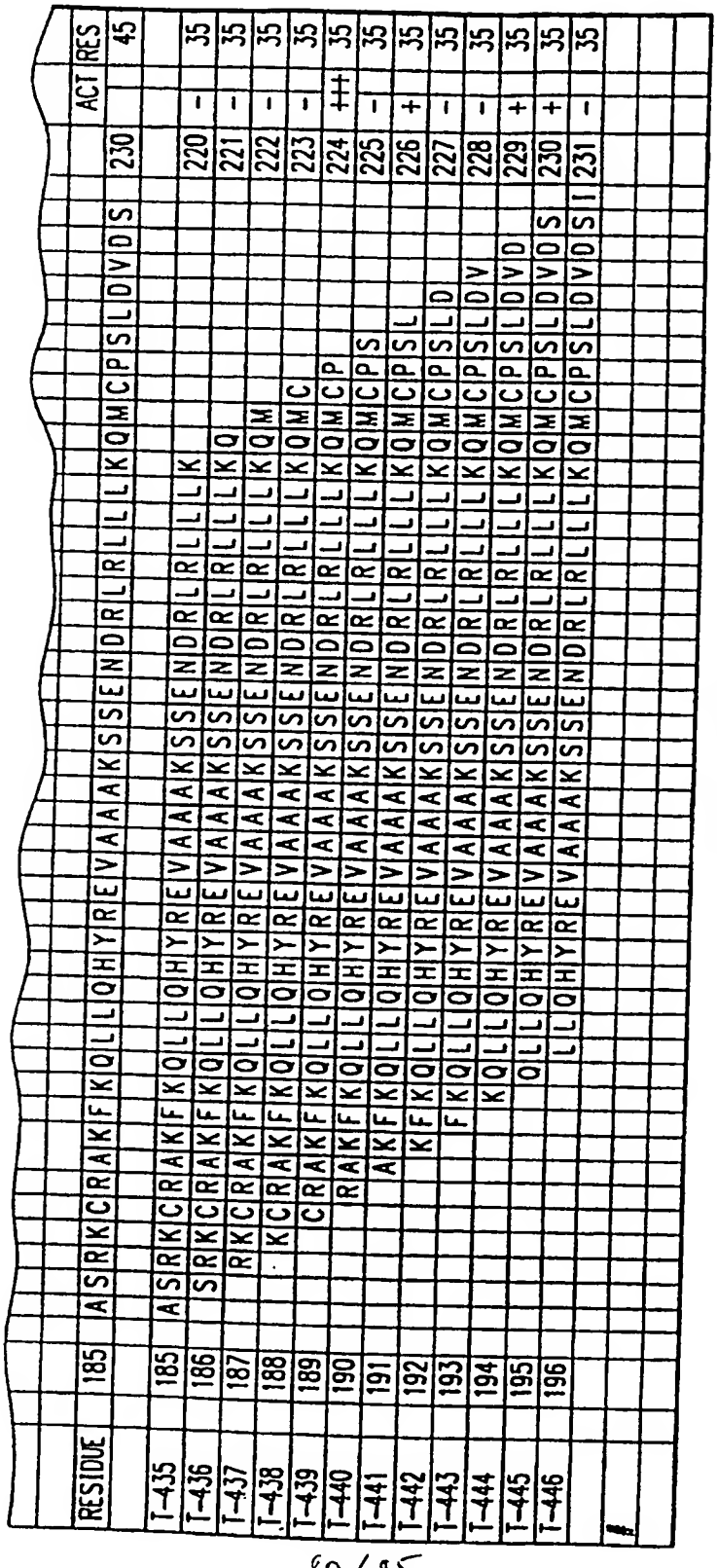


FIG.51B

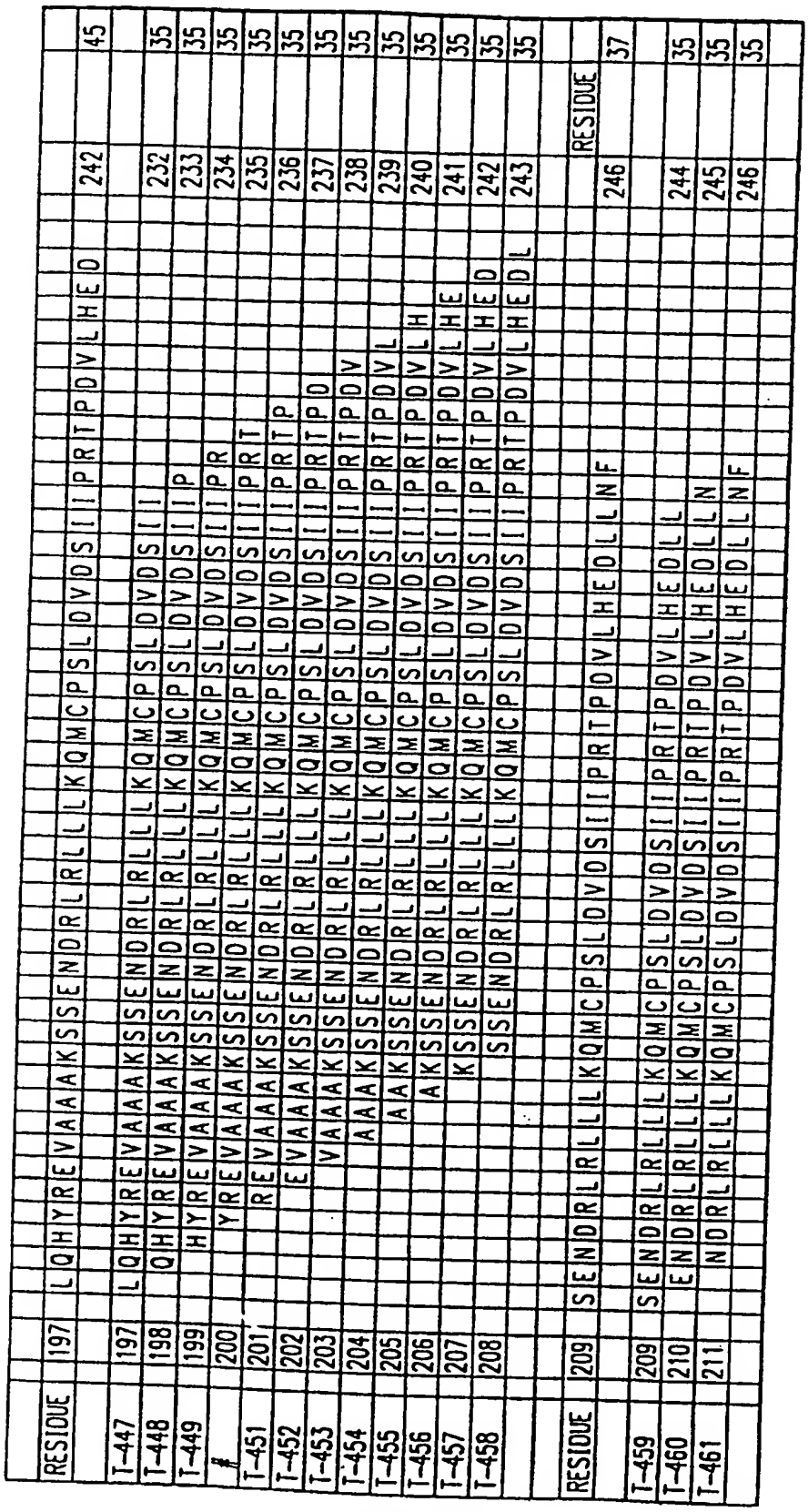


FIG.51C

DOMAIN I:

174 P-L-L-V-L-Q-A-G-F-F-L-L-T-R-I-L-T-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-G-T-T-V-C-L-G-Q-N-S-Q-S-P 220

P-L-L-V-L-Q-A-G-F-F-L-L-T-R-I-L-T-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T
L-L-V-L-Q-A-G-F-F-L-L-T-R-I-L-T-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T
L-V-L-Q-A-G-F-F-L-L-T-R-I-L-T-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V
V-L-Q-A-G-F-F-L-L-T-R-I-L-T-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C
L-Q-A-G-F-F-L-L-T-R-I-L-T-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C-L
Q-A-G-F-F-L-L-T-R-I-L-T-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C-L-G
A-G-F-F-L-L-T-R-I-L-T-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C-L-G-Q
G-F-F-L-L-T-R-I-L-T-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C-L-G-Q-N
F-F-L-L-T-R-I-L-T-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C-L-G-Q-N-S
F-L-L-T-R-I-L-T-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C-L-G-Q-N-S-Q
L-L-T-R-I-L-T-I-P-Q-S-L-D-S-W-W-T-S-L-N-F-L-G-G-T-T-V-C-L-G-Q-N-S-Q-S

FIG.52A

DOMAIN II:

223 P-G-Y-R-W-M-C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-T-S-T-G-P-C-R-T-C-M-T-T 291

P-G-Y-R-W-M-C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L
G-Y-R-W-M-C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P
Y-R-W-M-C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V
R-W-M-C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C
W-M-C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P
M-C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L
C-L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I
L-R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P
R-R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G
R-F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S
F-I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-G-G-S-S
I-I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-T

I-F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-T-S
F-L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-T-S-T
L-F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-T-S-T-G
F-I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-T-S-T-G-P
I-L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-T-S-T-G-P-C
L-L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-T-S-T-G-P-C-R
L-L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-T-S-T-G-P-C-R-T
L-C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-T-S-T-G-P-C-R-T-C
C-L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-T-S-T-G-P-C-R-T-C-M
L-I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-T-S-T-G-P-C-R-T-C-M-T
I-F-L-L-V-L-L-D-Y-Q-G-M-L-P-V-C-P-L-I-P-G-S-S-T-S-T-G-P-C-R-T-C-M-T-T

FIG.52B

		Fusion	T888
		IC50 µg/ml	IC50 Conc. (nM)
T112	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2	0.30	1
T800	Ac-AAASDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2	2.6	6.4
T801	Ac-VFPAAAFDASISQVNEKINQSLAFIRKSDELLHNV-NH2	1.7	Insoluble
T802	Ac-VFPSDEAAASISQVNEKINQSLAFIRKSDELLHNV-NH2	3	75.6
T803	Ac-VFPSDEFDAAAAQVNEKINQSLAFIRKSDELLHNV-NH2	2.1	7.3
T804	Ac-VFPSDEFDASISAAAEKINQSLAFIRKSDELLHNV-NH2	1.3	28.7
T805	Ac-VFPSDEFDASISQVNAAANQSLAFIRKSDELLHNV-NH2	2.1	
T806	Ac-VFPSDEFDASISQVNEKIAAALAFIRKSDELLHNV-NH2	0.9	3.5
T807	Ac-VFPSDEFDASISQVNEKINQSAAAIRKSDELLHNV-NH2	0.5	195
T808	Ac-VFPSDEFDASISQVNEKINQSLAFAAASDELLHNV-NH2	0.5	7.2
T809	Ac-VFPSDEFDASISQVNEKINQSLAFIRKAAALLHNV-NH2	3.8	Insoluble
T810	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDEAAANV-NH2	1.3	624
T811	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLAAA-NH2	1.6	4.8
T1669	Ac-VFPSDEADASISQVNEKINQSLAFIRKSDELLHNV-NH2		
T1670	Ac-VFPSDEFAASISQVNEKINQSLAFIRKSDELLHNV-NH2		
T1671	Ac-VFPSDEFDASISAVNEKINQSLAFIRKSDELLHNV-NH2		
T1672	Ac-VFPSDEFDASISQANEKINQSLAFIRKSDELLHNV-NH2		
T1673	Ac-VFPSDEFDASISQVAEKINQSLAFIRKSDELLHNV-NH2		
T1680	Ac-VFPSDEFDASISQVNEKINQSAAFIRKSDELLHNV-NH2		
T1681	Ac-VFPSDEFDASISQVNEKINQSLAAIRKSDELLHNV-NH2		
T1682	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDEALHNV-NH2		
T1683	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELAHNV-NH2		
T1684	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLANV-NH2		

FIG. 53

		Does Substitution prevent CD interaction?	Fusion IC50 (ng/mL)	T83 FILARA (Blot-T20) IC50 Conc. (nM)	T1342 FP (Fluo-T20) IC 50 Conc. (nM)
T20	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2	Native	2	69	
T813	Ac-AAAAIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2		3	1000	
T878	Ac-YTSAAASLIEESQNQQEKNEQELLELDKWASLWNWF-NH2	Reduced	37	1000	
T877	Ac-YTSLIHAAAEESQNQQEKNEQELLELDKWASLWNWF-NH2	Inhibited	1757	Neg	
T876	Ac-YTSLIHSLIAAAQNQQEKNEQELLELDKWASLWNWF-NH2	Native	11	29	
T875	Ac-YTSLIHSLIEESAAAQEKNEQELLELDKWASLWNWF-NH2	Inhibited	33	>3000	
T874	Ac-YTSLIHSLIEESQNQAAANEQELLELDKWASLWNWF-NH2	Inhibited	545	>3000	
T873	Ac-YTSLIHSLIEESQNQQEKAAAELLELDKWASLWNWF-NH2	Inhibited	814	Neg	
T872	Ac-YTSLIHSLIEESQNQQEKNEQAAAELDKWASLWNWF-NH2	Native	23	66	
T871	Ac-YTSLIHSLIEESQNQQEKNEQELLAAAKWASLWNWF-NH2	Inhibited	89	1156	
T870	Ac-YTSLIHSLIEESQNQQEKNEQELLELDAAASLWNWF-NH2	Reduced	8	251	
T869	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWAAAANTWF-NH2	Reduced	28	57	
T868	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWAAA-NH2	Reduced	56	56	
T1663	Ac-ATSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2	Native			
T1664	Ac-YASLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2	Native			
T1665	Ac-YTALIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2	Native			
T1660	Ac-YTSAIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2	Reduced			
T1661	Ac-YTSLAHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2	Reduced			
T1662	Ac-YTSLIASLIEESQNQQEKNEQELLELDKWASLWNWF-NH2	Native			
T1656	Ac-YTSLIHALIEESQNQQEKNEQELLELDKWASLWNWF-NH2	Native			
T1657	Ac-YTSLIHSAIEESQNQQEKNEQELLELDKWASLWNWF-NH2	Reduced			
T1659	Ac-YTSLIHSLAEESQNQQEKNEQELLELDKWASLWNWF-NH2	Inhibited			
T1653	Ac-YTSLIHSLIEESANQQEKNEQELLELDKWASLWNWF-NH2	Native			60
T1654	Ac-YTSLIHSLIEESQAQQEKNEQELLELDKWASLWNWF-NH2	Native			
T1655	Ac-YTSLIHSLIEESQNAQEKNEQELLELDKWASLWNWF-NH2	Inhibited			
T1650	Ac-YTSLIHSLIEESQNQAEKNEQELLELDKWASLWNWF-NH2	Inhibited			1000
T1651	Ac-YTSLIHSLIEESQNQQAKNEQELLELDKWASLWNWF-NH2	Native			14
T1652	Ac-YTSLIHSLIEESQNQQEANEQELLELDKWASLWNWF-NH2	Native			40
T1630	Ac-YTSLIHSLIEESQNQQEKAEQELLELDKWASLWNWF-NH2	Inhibited			>1000
T1631	Ac-YTSLIHSLIEESQNQQEKNAQELLELDKWASLWNWF-NH2	Reduced			200
T1632	Ac-YTSLIHSLIEESQNQQEKNEAELLELDKWASLWNWF-NH2	Native			27
T1627	Ac-YTSLIHSLIEESQNQQEKNEQELLALDKWASLWNWF-NH2	Native			27
T1628	Ac-YTSLIHSLIEESQNQQEKNEQELLEADKWASLWNWF-NH2	Reduced			250
T1629	Ac-YTSLIHSLIEESQNQQEKNEQELLELAKWASLWNWF-NH2	native			53

FIG. 54

INTERNATIONAL SEARCH REPORT

Inte. .ional application No.
PCT/US00/35727

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C12Q 1/70; G01N 33/53; A61K 38/00, 39/21
US CL :435/5, 7.1; 530/300; 424/188.1, 208.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/5, 7.1; 530/300; 424/188.1, 208.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPATFUL, WPIDS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEN, C.-H., et al., A Molecular Clasp in the Human Immunodeficiency Virus (HIV) Type 1 TM Protein Determines the Anti-HIV Activity of gp41 Derivatives: Implication for Viral Fusion. J. Virol. June 1995. Vol. 69. No. 6. pages 3771-3777, see entire document.	1-3
Y	US 5,656,480 A (WILD et al.) 12 August 1997, see entire document.	1-3
Y	US 5,464,933 A (BOLOGNESI et al.) 07 November, 1995, see entire document.	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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